

# ANNALS OF INTERNAL MEDICINE

Published Monthly by The American College of Physicians

VOL. 54, NO. 5



NOVEMBER, 1959

## Contents

	Page
Concerning the Functions and Nomenclature of Blood Clotting Factors, with a Preliminary Report of the Profile of Blood Clotting Factors in Young Males. IRVING S. WRIGHT .....	541
Studies of Poststreptococcal Nephritis and Other Glomerular Diseases. DAVID P. EARLE and ROBERT B. JENNINGS .....	851
The Pathogenesis of Leptospiroid Jaundice. F. RAMOS-MORALES, R. S. DIAZ-RIVERA, A. MCINTOSH-RIVERA, JOSÉ A. RULLÁN, A. S. BENJAMINSON and JOSEFINA ACOSTA-MATÍEZ .....	861
A Critical Analysis of the Use of Salicylazosulfapyridine in Chronic Ulcerative Colitis. CHARLES G. MOERTEL and J. ARNOLD BARGEN .....	879
Some Unusual Syndromes Associated with Neoplastic Disease. G. LENNARD-GOLD and BRUCE I. SHNIDER .....	890
The Diagnosis and Classification of Mediastinal Masses. I. A Study of 782 Cases. HAROLD A. LYONS, GEORGE L. CALVY and BILLY P. SAMMONS .....	897
Familial Hodgkin's Disease: Its Significance and Implications. DENNIS V. RAZIS, HENRY D. DIAMOND and LLOYD F. CRAVEN .....	933
Effects of Long-Term Estrogen Therapy on Serum Cholesterol and Phospholipids in Men with Myocardial Infarction. JESSIE MARMORSTON, FREDERICK J. MORSE, OSCAR MALIBSON, OLIVER KUZMA and JACK J. LEWIS .....	972
Use of Trimethidinium Methosulfate (A New Ganglionic Blocking Agent) in the Treatment of Hypertension. NEMAT O. BORHANI .....	983
Newer Physiology of Absorption from the Intestine. RICHARD J. REITZMEIER .....	993
Factors Controlling Hemopoiesis: Experimental Observations on Their Role in Polycythemia Vera. JAMES W. LINMAN, FRANK H. BETHELL and MARTHA J. LONG .....	1003
Clinical Observations Regarding Xanthelasma. JOSEPH B. VACCA, WILLIAM A. KNIGHT, JR. and GORDON W. O. BROUW, Sr. ....	1019
Drugs in Emotional Disorders: Past and Present. LEO E. HOLLISTER .....	1032
Marfan's Syndrome and the Weill-Marchesani Syndrome in the S. Family. DORANCE BOWEN .....	1049
Case Reports:	
The Diagnosis of Acute Viral Hepatitis Simulating an Abdominal Emergency. ELLIS L. ROBERT and MARVIN H. SLEISINGER .....	1071
Familial Congenital Methemoglobinemia: Report of a Case and Family Study. H. E. DEFARE and M. J. HICKMAN .....	1078
Chronic Radiation Nephritis: A Review of the Literature with Report of a Case. JAMES A. JENNISON .....	1084
Infectious Mononucleosis in the Aged. CHARLES M. SHAPIRO and HARVEY HORWITZ .....	1092
Localized Pretibial Myxedema: Report of Two Cases Treated with Hydrocortisone by Local Injection. RICHARD W. DYKE, CLAYTON E. WOOD and SOPHOCLES D. MARTY .....	1097
Pulmonary Paragonimiasis. DONALD H. HARTER and STEPHEN I. ALLEN .....	1104
Editorial—Changing Concepts of the Pathogenesis of Wilson's Disease .....	1110
Reviews .....	1116
College News Notes .....	cy

Nothing is Quicker\*

Nothing is more Effective\*

# In Asthma

PREMICRONIZED FOR  
OPTIMAL  
EFFICACY

\* Spirograms show  
22½% improvement in vital  
capacity within moments after  
inhalation of Medihaler medication.

Recorded in the Lung Station (Tubes)  
at the Boston City Hospital.  
Maurice B. Segal, M.D., Director.

Available  
with either  
isoproterenol  
or epinephrine.

Automatically measured-dose  
aerosol medications.

Nonbreakable... Shatterproof  
Spillproof... Leakproof

## Medihaler-ISO®

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.

## Medihaler-EPI®

Epinephrine bitartrate, 5.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

NOTABLY WELL TOLERATED AND EFFECTIVE FOR CHILDREN, TOO



Northridge, Calif.

Subscription per annum, not postpaid, \$10.00, United States, Canada, Hawaii, and Puerto Rico;  
\$11.00, other countries.

Second-class postage paid at Lancaster, Pa.

*"Curiosity is one of the  
permanent and certain characteristics  
of a vigorous mind."* Dr. Samuel Johnson

*Sam: Johnson.*



No matter how much a man knows about his profession, there is always more he can read with profit and enjoyment.

**Recommended for your library**  
**KEITH-ROWE-VLAD: HEART DISEASE IN INFANCY AND CHILDHOOD, 1958, 877 pages, 360 illustrations**

"an invaluable book...and a stimulating and useful one for the internist"  
—*Annals of Internal Medicine* \$22.50

**HAUGEN-DIXON-DICKEL: A THERAPY FOR ANXIETY TENSION REACTIONS, 1958, 110 pp.**

"This excellent monograph offers one practical and successful method for treating psychosomatic illness in everyday office practice."

—*Military Medicine* \$3.50

**RISEMAN-SAGALL: ELECTROCARDIOGRAM CLINICS, 1958, 259 pages, illustrated**

"recommended to those interested in the correct diagnosis of cardiovascular disease"  
—*Journal of the American Medical Association* \$10.50

*The Macmillan Company* 60 Fifth Avenue, New York 11, N. Y.

Please Mention this Journal when writing to Advertisers



## A good day's work without fear of angina ...on *Metamine<sup>®</sup> Sustained, b.i.d.*<sup>1</sup>

This normally active angina patient who can do a satisfying day's work without discomfort or the dread of a severe attack is typical of those controlled by METAMINE<sup>®</sup> SUSTAINED—aminotrate phosphate, 10 mg. (Leeming). A simple protective medication (1 tablet on arising and 1 before the evening meal), METAMINE SUSTAINED eliminates anginal episodes altogether, or greatly reduces their severity and frequency. Many patients refractory to other drugs of this type are aided by METAMINE SUSTAINED<sup>2</sup>.

Moreover, relative freedom from side effects typical of many cardiac nitrates (headache, nausea,

hypotension) permits angina-preventive medication with METAMINE SUSTAINED for indefinite periods. And, when you prescribe METAMINE SUSTAINED, b.i.d., your angina patient will need less nitroglycerin and thus remain fully responsive to this vital emergency medication.

**Supplied:** bottles of 50 and 500 sustained-release tablets. Also: METAMINE (2 mg.); METAMINE (2 mg.) WITH BUTABARBITAL ( $\frac{1}{4}$  gr.); METAMINE (10 mg.) WITH BUTABARBITAL ( $\frac{1}{4}$  gr.) SUSTAINED; METAMINE (10 mg.) SUSTAINED WITH RESERPINE (0.1 mg.).

*Theo. Leeming & Co. Inc.* New York 17.



1. Einfeldt, H.W.: Case history 18/35. Pers. comm. 2. Fuller, H.L. and Kassel, L.E.: Antibiotic Med. & Clin. Therapy, 3:322, 1956.

## New!—BIOPSY MANUAL by Hardy, Griffin and Rodriguez

How to safely obtain specimens of tissue from each area of the body

This beautifully illustrated manual gives you the safest step-by-step techniques for obtaining suitable specimens of tissue from virtually any area of your patient's body. With the help of crystal clear drawings, the authors describe incisions, landmarks, anesthesia, pitfalls and complications. Internists will learn here exactly how to obtain the material the pathologist needs for diagnosis, for prognosis, and for following the course and effectiveness of therapy in cancer and other conditions.

By JAMES D. HARDY, M.D., Professor and Chairman of the Department of Surgery; JAMES C. GRIFFIN, JR., M.D., Assistant Instructor in Surgery, Administrative Chief Resident in Surgery, National Cancer Institute Trainee; and JORGE A. RODRIGUEZ, M.D., Assistant Professor of Surgical Anatomy—All at the University of Mississippi School of Medicine. 150 pages, 6" x 9 1/4", with 142 illustrations on 54 figures. \$6.50. *New!*



## New!—HANDBOOK OF CIRCULATION

Sponsored by the National Research Council—packed with useful facts

More than 300 eminent contributors have supplied the material for this valuable reference to give you today's known *quantitative* data on circulation. Information is well organized in tables, graphs, diagrams and drawings. It covers such areas as: cardiac output; heart rate; blood pressures; chemical composition and physical properties of heart and great vessels; the electrocardiogram; heart sounds and murmurs; blood coagulants and anticoagulants; effects of: pregnancy, decompression, radiation, drugs, and pathologic conditions on circulation; etc.

Analyzed and compiled by PHILIP L. ALTMAN. Edited by DOROTHY S. DITTMER and RUDOLPH M. GREBE. Prepared under Direction of the Committee on the Handbook of Biological Data, Division of Biology and Agriculture, National Academy of Sciences, National Research Council. 393 pages, 8 1/2" x 11". \$7.50. *New!*



## New (8th) Edition!—Ochsner & DeBakey CHRISTOPHER'S MINOR SURGERY

An up-to-date and c'early illustrated guide to "office surgery"

This practical book discusses only those surgical conditions which can be treated in your office, in the patient's home, or in an outpatient clinic. For each disorder eminent authorities briefly discuss etiology, pathology and diagnosis. "How-to-do-it" instructions for therapy follow. Important changes have been made throughout the book for this edition including: technique of stellate ganglion block, aspiration of mammary cysts, new help on arteriosclerosis, conservative treatment of acute arterial occlusion, etc.

By 23 Contributors. Edited by ALTON OCHSNER, M.D., F.A.C.S., Professor of Clinical Surgery, Tulane University School of Medicine; and MICHAEL E. DEBAKEY, M.D., F.A.C.S., Professor of Surgery and Chairman of the Department of Surgery, Baylor University College of Medicine. 539 pages, 6 1/4" x 10", with 298 illustrations. \$10.50.

*New (8th) Edition*



ORDER TODAY!

W. B. SAUNDERS Company, West Washington Square, Philadelphia 5

AIM 11-59

- |   |         |
|---|---------|
| <input type="checkbox"/> Hardy, Griffin & Rodriguez' Biopsy Manual.....     | \$6.50  |
| <input type="checkbox"/> Handbook of Circulation.....                       | \$7.50  |
| <input type="checkbox"/> Ochsner & DeBakey—Christopher's Minor Surgery..... | \$10.50 |

Name.....

Address.....

Please Mention this Journal when writing to Advertisers

## LIFE STORY

The leading site of cancer today is the colon and rectum. In 1958, 58,000 new cases were diagnosed.

The present 5-year survival rate for these cancers is less than 30%. This figure could be greatly increased by closing the very wide gap between *actual* and *possible* survival rates.

Earlier diagnosis is an immediate requirement. The American Cancer Society urges annual health checkups for all adults, and employment of digital and proctoscopic examinations of the rectum and colon by physicians, to find cancer in an early stage.

AMERICAN CANCER SOCIETY



## WANTED

### Back Issues of ANNALS OF INTERNAL MEDICINE

Good used copies of the following issues are now needed. Only those issues which are currently being advertised will be accepted.

\$1.50 each for

Vol. 1, No. 1—July, 1927  
Vol. 1, No. 2—August, 1927  
Vol. 1, No. 5—November, 1927  
Vol. 1, No. 7—January, 1928  
Vol. 2, No. 5—November, 1928

\$1.00 each for

Vol. 6, No. 9—March, 1933

75¢ each for

Vol. 46, No. 2—February, 1957  
Vol. 49, No. 3—September, 1958  
Vol. 49, No. 4—October, 1958  
Vol. 50, No. 1—January, 1959  
Vol. 50, No. 2—February, 1959

Address Journals to:

E. R. LOVELAND, Executive Secretary  
4200 Pine Street Philadelphia 4, Pa.

*Helps You Solve Your Clinical Problems—Quickly!*

## THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

*"The Yellow Journal"*

- ★ Introductory Offer to New Subscribers: 8 Months for \$6.
- ★ Special ½ Price Offer to Residents & Interns: 1 Year for \$5.

*Original, Authoritative Papers, plus the Monthly "Progress of Medical Science" Covering All of the Specialties*

LEA & FEBIGER 600 Washington Square, Philadelphia 6, Pa.

Enclosed is \$..... in payment of my subscription (as indicated below) to THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

U. S. and Possessions: ☐ Special Trial Subscription, 8 months for \$6.00  
☐ 1 Year \$10.00 ☐ 2 Years \$18.00 ☐ 3 Years \$27.00  
☐ Residents and Interns Only (½ Price) 1 Year \$5.00  
 Canada ☐ 1 Year \$10.50 All Other Countries ☐ 1 Year \$12.00

NAME (print).....

ADDRESS.....

If Intern or Resident, Give Hospital Affiliation: .....

AIM 11-59

Please Mention this Journal when writing to Advertisers



## Important New Books from HOEBER-HARPER

### ROSENBAUM & BELKNAP'S *Work and the Heart*

● Now for the first time today's knowledge of the influence of work, exercise, and stress on cardiac function is brought together in one place. Seventy-four experts from many fields—internists, cardiologists, pathologists, physiologists, biophysicists, industrial medicine specialists, lawyers, and many others—contribute their special knowledge to put at your disposal a wealth of information. Much of it is new data published here for the first time. The book covers a tremendous range of topics conveniently organized in five parts: basic physiology, clinical physiology, pathology, work classification, and workmen's compensation. Sponsorship by the American Heart Association, the National Health Institute, and the Industrial Health Council of the A.M.A. is your guarantee of the calibre of the book's contents.

*Edited by FRANCIS F. ROSENBAUM, M.D., Associate Clinical Professor of Medicine and ELSTON L. BELKNAP, M.D., Professor and Director, Department of Occupational and Environmental Medicine, Marquette University School of Medicine.* 559 pages, 207 illus., \$12.00

### WAIFE & SHAPIRO'S *The Clinical Evaluation of New Drugs*

● Fourteen authorities explain how to carry out the clinical trial and how to judge the reports. An essential book for every physician who ever prescribes a new pharmaceutical. Here you will find full discussions of the role of the investigator, placebos, recognition of the potential variables in a clinical trial and how to control them, human experimentation, planning the experimental design, when *double blind* technic is essential and when *single blind* is adequate, and the actual conduct of clinical trials in specific areas of medicine.

*Edited by S. O. WAIFE, M.D., Associate in Medicine, Indiana University Medical School and ALVIN P. SHAPIRO, M.D., Assistant Professor, Departments of Clinical Science and Medicine, University of Pittsburgh School of Medicine.* 223 pages, \$7.50

### DURHAM'S *Encyclopedia of Medical Syndromes*

● A unique, encyclopedic reference of nearly 1,000 syndromes . . . the indispensable companion to your medical dictionary. This work fills a need that has long existed in the literature of the profession. It is completely up to date, and in the number of syndromes it offers and in the fullness of its descriptions it far exceeds any work on the subject published to date. The syndromes—both eponymic and descriptive—have been gleaned from a wide variety of sources. Synonyms for each syndrome described are given as are closely related subjects.

*By ROBERT H. DURHAM, M.D., F.A.C.P., Physician-in-Charge, Division of General Medicine, Henry Ford Hospital, Detroit, Michigan.* \$13.50

—SEND ON APPROVAL—

PAUL B. HOEBER, Inc., MEDICAL BOOK DEPARTMENT OF HARPER & BROTHERS  
49 East 33rd Street, New York 16, New York

Please send me on approval the books checked:

- ☐ ROSENBAUM & BELKNAP'S *Work and the Heart* . . . . . \$12.00  
☐ WAIFE & SHAPIRO'S *The Clinical Evaluation of New Drugs* . . . \$7.50  
☐ DURHAM'S *Encyclopedia of Medical Syndromes* . . . . . \$13.50  
☐ My check is enclosed (return privileges) ☐ Bill me

NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_

AIM 11/50

Please Mention this Journal when writing to Advertisers

## Cancer in Families

A STUDY OF THE RELATIVES OF  
200 BREAST CANCER PROBANDS

By DOUGLAS P. MURPHY, M.D.,  
and HELEN ABBEY, Sc.D.

This book summarizes a field investigation set up to determine whether or not cancer occurs with any unusual frequency among the blood relatives of an individual who suffers from cancer of the breast. A series of 200 families in which a member suffered from breast cancer was interviewed and additional information was secured from family physicians, hospitals, undertakers, and bureaus of vital statistics. One hundred and ninety-eight control families were also investigated.

The resulting information, here tabulated and analyzed, is based upon approximately 6,000 relatives in each of the two groups. The data reveal no evidence for any unusual frequency of cancer—of the breast or elsewhere—among the relatives of breast cancer patients.

This study differs significantly from other family surveys dealing with cancer occurrence in that the study population was interviewed once with regard to female relatives, and a second time (by the same investigators) with regard to male relatives.

The second half of the survey also made it possible to check on the completeness and accuracy of the original observations. \$2.50

A COMMONWEALTH  
FUND BOOK

Through your bookseller, or



HARVARD UNIVERSITY  
PRESS

79 Garden Street,  
Cambridge 38, Massachusetts



## ADVANCED ELECTROCARDIOGRAPHY COMPLEX ARRHYTHMIAS

L. N. KATZ, R. LANGENDORF  
and A. PICK

MICHAEL REESE  
HOSPITAL  
AND MEDICAL CENTER

December 7-11, 1959

Differential diagnosis of arrhythmias based on fundamental physiological concepts. Tuition: \$100.00.

*For further information write:*

Cardiovascular Department  
Michael Reese Hospital  
and Medical Center  
Chicago 16, Illinois

## FUTURE ANNUAL SESSIONS

1960—San Francisco, Calif.,  
April 4-8

1961—Bal Harbour, Fla.,  
May 8-12

1962—Philadelphia, Pa.,  
April 9-13

Please Mention this Journal when writing to Advertisers

**ACID TYPES** *from the Gelusil Family Album***UNCLE MILO**

By and large, ace firefighter Uncle Milo fed his ulcers per doctor's orders. But sometimes there he was . . . face to face with some forbidden delicacy. Then a single indiscretion, in a weak moment, was all it took to put him out of action.

Today, though, whatever the will-power of your ulcer patients, you can provide lastingly effective pain relief and acid control with Gelusil . . . the antacid adsorbent Uncle Milo should have had.

*Especially important to your hospitalized patients . . . Gelusil is all antacid in action . . . contains no laxative . . . does not constipate. The choice of modern physicians, for every antacid need.*

**GELUSIL®***the physician's antacid*

Blood pressure  
before Apresoline-Esidrix:

**206/118**  
mm.Hg\*

Blood pressure  
after Apresoline-Esidrix:

**182/98** mm. Hg\*

Added benefits: Lowered dosage requirements, fewer side effects • Improved renal blood flow • Relaxed cerebral vascular tone • Excellent diuresis in decompensated cases

SUPPLIED: Apresoline-Esidrix Tablets (orange), each containing 25 mg. of Apresoline hydrochloride and 15 mg. of Esidrix; bottles of 100.

\*Response of 56-year-old female patient noted in clinical report to CIBA.

APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA) / ESIDRIX® (hydrochlorothiazide CIBA)

**Apresoline-Esidrix®**  
Combination Tablets

POTENTIATED ANTIHYPERTENSIVE  
FOR ADVANCING HYPERTENSION



4/5008 MK

Please Mention this Journal when writing to Advertisers

New multiple action for chronic constipation

## COMBINACE\* tablets

Calcium and sodium alginate, dioctyl sodium sulfosuccinate and anthraquinone derivatives from cascara, Mead Johnson

combined ingredients for coordinated bowel conditioning

- prevents and corrects hard stools
- provides smooth "hydrasorbent" bulk
- provides gentle peristaltic stimulation

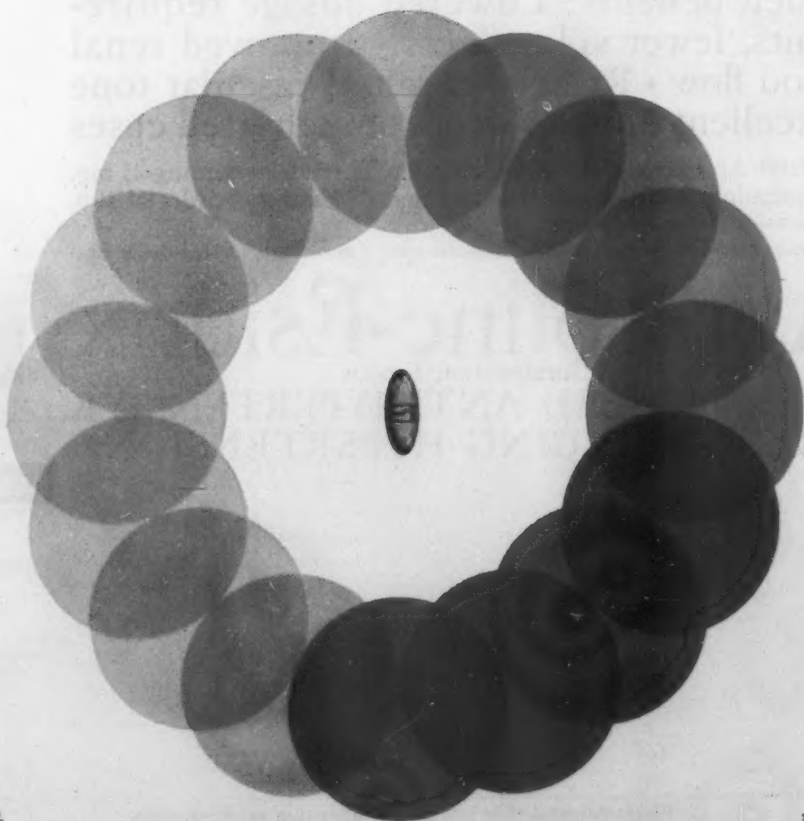
Only one to three Combinace tablets daily provide effective relief for the problem of chronic constipation. As Feightner states, "A new laxative agent, Combinace, combining...stool softening action...with a mild peristaltic stimulant and an effective hydrasorbent bulking agent, was an effective laxative agent in the treatment of chronically constipated, habitual cathartic users."<sup>1</sup>

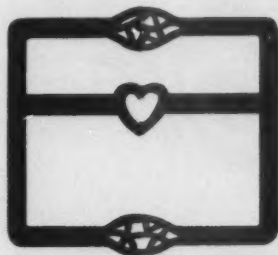
Mead Johnson & Company, Evansville 21, Indiana

1. Feightner, R. L.: J. Indiana M. A. 51:1672-1674 (Dec.) 1958.



Mead Johnson  
*Symbol of service in medicine*





FOR GREATER  
LATITUDE  
IN SOLVING  
THE PROBLEM  
HYPERTENSION  
WITHOUT  
SIGNIFICANT  
POTASSIUM  
DEPLETION

NEW

**RAUTRAX**

RAUDIXIN (Squibb standardized whole root Rauwolfia Serpentina) / ADEMOL (Squibb Flumethiazide) / POTASSIUM CHLORIDE

\*RAUDIXIN®, \*RAUTRAX® AND \*ADEMOL® ARE SQUIBB TRADEMARKS

**RAUTRAX**, a combination of Raudixin with Ademol (flumethiazide)—the new, safe nonmercurial diuretic—controls all degrees of hypertension. Elimination of excess extracellular sodium and water is rapid and safe.<sup>1-5</sup> Potassium loss is less than with other nonmercurial diuretics;<sup>1-3</sup> and, in addition, Rautrax increases protection against potassium and chloride depletion during long-term management by including supplemental potassium chloride.

The dependable diuretic action of Ademol rapidly controls the clinical and subclinical edema often associated with cardiovascular disease. And after Rautrax has normalized the fluid balance, the normal serum electrolyte pattern is not altered appreciably by continued administration.<sup>4</sup> Ademol also potentiates the antihypertensive action of Raudixin.<sup>1</sup> In this way a lower dose of each component controls hypertension effectively and safely . . . with fewer side effects.

REFERENCES: 1. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: *New England J. Med.* 260:872 (April 23) 1959. 2. Fuchs, M.; Bodi, T., and Moyer, J. H.: *Am. J. Cardiol.* 3:676 (May) 1959. 3. Fuchs, M., and others: *Monographs on Therapy* 4:43 (April) 1959. 4. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: *Am. Heart J.* 57:484 (April) 1959. 5. Rochelle, J. B., III; Montero, A. C., and Ford, R. V.: *Antibiotic Med. & Clin. Ther.* 5:267 (May) 1959. LITERATURE AVAILABLE ON REQUEST

**SQUIBB**



Squibb Quality—  
the Priceless Ingredient

Please Mention this Journal when writing to Advertisers

## Resident

It's been a long haul, but Walter Gammage, M.D., is far better at counting the days ahead than the days behind. Just a few months now, and his two-year pediatric residency will be over. Lately, for the first time in his life, Dr. Gammage has been estimating his target date for private practice on a calendar he can see and needn't imagine.

Dr. Gammage's residency duties don't give him much time to think about the coming Board examinations and the hoped-for certification. There are the morning rounds and new patients to see and examine. And the conferences with troubled parents. And, with it all, the teaching, the Grand Rounds, and the incessant studying on-duty and off.

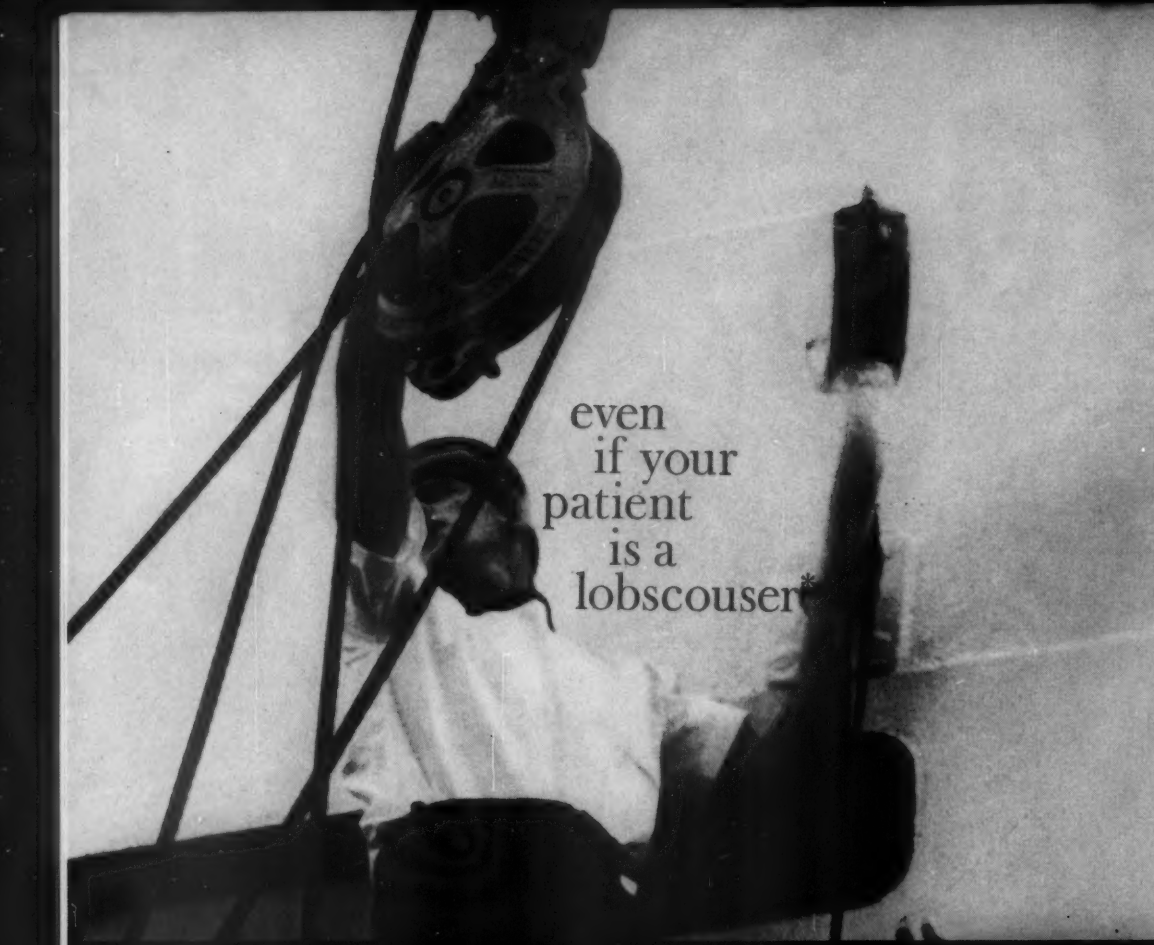
Dr. Gammage is married. Off-duty to him is time shared with the need to qualify for the most demanding of all professions. Both Dr. Gammage and his wife know it can't be any other way. They reckon the costs of long preparation in delayed fullness of family life, in delayed income, in delayed repayment of loans. They remember the crushing financial burdens that threatened to halt training after internship, without pediatric residency.

Dr. Gammage (that isn't his real name) is one of many objectively selected and highly qualified recipients of Wyeth Pediatric Residency Fellowships, providing \$2400 yearly for two years of residency training. From the Wyeth Fund for Postgraduate Medical Education, these awards and others are intended to encourage and strengthen the human resources at the service of medicine.



Philadelphia 1, Pa.





even  
if your  
patient  
is a  
lobscouser\*

he'll be under way again soon, once he's on

**PARAFON**<sup>®</sup>

(PARAFLEX<sup>®</sup> + TYLENOL<sup>®</sup>)

for muscle relaxation plus analgesia

and in arthritis

**PARAFON**<sup>®</sup>  
with Prednisolone

**McNEIL**

McNeil Laboratories, Inc. • Philadelphia 32, Pa.

prescribe PARAFON in low back pain—sprain—  
strains—rheumatic pains.

Each PARAFON tablet contains:

PARAFLEX<sup>®</sup> Chlorzoxazone† 125 mg.

Specific for skeletal muscle spasm.

TYLENOL<sup>®</sup> Acetaminophen 300 mg.

The analgesic preferred in musculoskeletal pain.

*Dosage:* Two tablets t.i.d. or q.i.d.

*Supplied:* Tablets, scored, pink, bottles of 30.

Each PARAFON WITH PREDNISOLONE tablet contains:

PARAFLEX<sup>®</sup> Chlorzoxazone† 125 mg., TYLENOL<sup>®</sup>

Acetaminophen 300 mg., and prednisolone 1.0 mg.

*Dosage:* One or two tablets t.i.d. or q.i.d.

*Supplied:* Tablets, scored, buff colored, bottles of 30.

*Precautions:* The precautions and contraindications  
that apply to all oral steroids should be kept in mind  
when prescribing PARAFON WITH PREDNISOLONE.

\*Patent

†U.S. Patent Pending

In hypoprothrombinemia

# KONAKION

**Rapid action**

rate of absorption faster than menadione or derivatives...more potent and lasting effects.

**Wide margin of safety**

substantially safer than vitamin-K analogues—no kernicterus reported.

**Versatility of administration**

capsules for oral use...fine aqueous dispersion for parenteral administration.

**Compatibility**

unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.

**Low dosage forms**

no excess, no waste—packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired.

KONAKION®—brand of vitamin K<sub>1</sub>

ROCHE® Capsules—5 mg; Ampuls—1 mg/0.5 cc; 10 mg/1 cc; 25 mg/2.5 cc

# STOP BLEEDING

ROCHE LABORATORIES—Division of Hoffmann-La Roche Inc—Nutley 10, New Jersey

# LEDERLE INTRODUCES... a masterpiece



## greater antibiotic activity

Milligram for Milligram, DECLOMYCIN exhibits 2 to 4 times the activity of tetracycline against susceptible organisms. (Activity level is the basis of comparison—not quantitative blood levels—since action upon pathogens is the ultimate value.\*) Provides significantly higher serum activity level...

## with far less antibiotic intake

DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents.

## unrelenting peak antimicrobial attack


The DECLOMYCIN high activity level is uniquely constant throughout therapy. Eliminates peak-and-valley fluctuation, favoring continuous suppression. Achieved through remarkably greater stability in body fluids, resistance to degradation and a low rate of renal clearance.

\*Hirsch, H. A., and Finland, M.:  
*New England J. Med.*  
260:1099 (May 28) 1959.

# DECLO

Demethylchlortetracycline Lederle

# e of antibiotic design



plus  
"extra-  
day"  
activity  
FOR PROTECTION  
AGAINST  
RELAPSE

DECLOMYCIN maintains activity for one to two days after discontinuance of dosage. Features unusual security against resurgence of primary infection or secondary bacterial invasion—two factors often resembling a "resistance problem"—enhancing the traditional advantages of tetracycline... for greater physician-patient benefit in the distinctive, dry-filled, duotone capsule

immediately available as:  
DECLOMYCIN  
Capsules, 150 mg.,  
bottles of 16 and 100.  
Adult dosage: 1 capsule  
four times daily.

# MYCIN<sup>®</sup>



LEDERLE LABORATORIES  
a Division of  
AMERICAN CYANAMID COMPANY  
Pearl River, New York

Does more than curb appetite...  
also relieves the tensions of dieting



new!

# Appetrol<sup>®</sup>

DEXTRO-AMPHETAMINE + MILTOWN<sup>®</sup>

Helps you keep your patient  
on your diet

AN EXTENSIVE SURVEY shows that in 68% of overweight persons there is an emotional basis for failure to limit food intake.<sup>1</sup> Appetrol has been formulated to help you overcome this problem and to keep your overweight patient on your diet.

THIS NEW ANORECTIC does more than give you dextro-amphetamine to curb your patient's appetite. It also gives you Miltown to relieve the tensions of dieting which undermine her will power.


IN PRESCRIBING APPETROL, you will find that your patient is relaxed and more easily managed so that she will stay on the diet you prescribe.

**Usual dosage:** 1 or 2 tablets one-half to 1 hour before meals.

**Each tablet contains:** 5 mg. dextro-amphetamine sulfate and 400 mg. Miltown (meprobamate, Wallace).

**Available:** Bottles of 50 pink, uncoated tablets.

1. Kotkov, B., Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, October 1958.

 WALLACE LABORATORIES, New Brunswick, N. J.

CPL-318

first in preference for relief from cough

quiets the cough and calms the patient

Expectorant  
Antihistaminic

Sedative  
Topical anesthetic

**PHENERGAN®**

EXPECTORANT



Promethazine Expectorant, Wyeth  
with Codeine Plain (without Codeine) Philadelphia 1, Pa.

**NEW NON-NARCOTIC FORMULA**

Pediatric **PHENERGAN** EXPECTORANT  
with Dextromethorphan, Wyeth



*For the first time*

## CONVENIENCE and ECONOMY

*for that all-important first dose  
of broad-spectrum antibiotic therapy*

*New*

**TERRAMYCIN<sup>®</sup>**

brand of oxytetracycline

## INTRAMUSCULAR SOLUTION

Initiation of therapy in minutes after diagnosis with new,  
ready-to-inject Terramycin Intramuscular Solution provides maximum,  
sustained absorption of potent broad-spectrum activity.

*...and for continued, compatible,  
coordinated therapy*

## COSA-TERRAMYCIN<sup>®</sup>

oxytetracycline with aluminum hydroxide

## CAPSULES

Continuation with oral Cosa-Terramycin every six hours will  
provide highly effective antibacterial serum and tissue levels for  
prompt infection control.

The unsurpassed record of clinical effectiveness and safety established for  
Terramycin is your guide to successful antibiotic therapy.

**Supply:**

**Terramycin Intramuscular Solution<sup>®</sup>**

100 mg./2 cc. ampules      250 mg./2 cc. ampules

**Cosa-Terramycin Capsules**

125 mg. and 250 mg.

Cosa-Terramycin is also available as:

Cosa-Terramycin Oral Suspension — peach flavored,  
125 mg./5 cc., 2 oz. bottle

Cosa-Terramycin Pediatric Drops — peach flavored,  
5 mg./drop (100 mg./cc.), 10 cc. bottle with plastic calibrated dropper

Complete information on Terramycin Intramuscular Solution and  
Cosa-Terramycin oral forms is available through your Pfizer Representative  
or the Medical Department, Pfizer Laboratories.

Contains 2% Xylecaine<sup>®</sup> (lidocaine), trademark of Astra Pharmaceutical Products, Inc.

**Pfizer** Science for the world's well-being<sup>™</sup>

**PFIZER LABORATORIES**, Division, Chas. Pfizer & Co.

Brooklyn 6, N. Y.

*in peptic ulcer...*

**KEEPS THE MIND  
OFF THE STOMACH  
...THE STOMACH  
FREE OF PAIN**



*direct antispasmodic action plus control of anxiety and tension*

**NOW...**

*2 Milpath forms  
for adjustability  
of dosage*

**MILPATH-400**—Yellow, scored tablets of 400 mg. meprobamate and 25 mg. tridihexethyl chloride (formerly supplied as the iodide). Bottle of 50.

**DOSAGE:** 1 tablet t.i.d. at mealtime and 2 at bedtime.

**MILPATH-200**—Yellow, coated tablets of 200 mg. meprobamate and 25 mg. tridihexethyl chloride. Bottle of 50.

**DOSAGE:** 1 or 2 tablets t.i.d. at mealtime and 2 at bedtime.

# Milpath

**\*Miltown + anticholinergic**

**WALLACE LABORATORIES** New Brunswick, N. J.



**selective peripheral action to relieve  
symptoms of arterial insufficiency<sup>1</sup>—**

intermittent claudication

leg pain

coldness and numbness of extremities

in

Arteriosclerosis Obliterans

Diabetic Vascular Disease

Buerger's Disease


Thrombophlebitis

**NEW**

**VASODILAN<sup>®</sup>**

Pronounced VĀ-ZŌ-DY-LAN

Isosuprine hydrochloride, Mead Johnson

a myo--vascular relaxant

**brings blood to the deep tissues by  
direct action on the arterial wall<sup>1,2</sup>**

**with** remarkable safety in recommended doses<sup>1-7</sup>

**without** adverse effects on coronary flow<sup>1,2</sup>

**without** troublesome hypotension or tachycardia<sup>1,2</sup>

**without** renal effects<sup>1,2</sup>

**without** increase in gastric acidity<sup>2</sup>

**without** ganglionic blocking action<sup>1-3</sup>

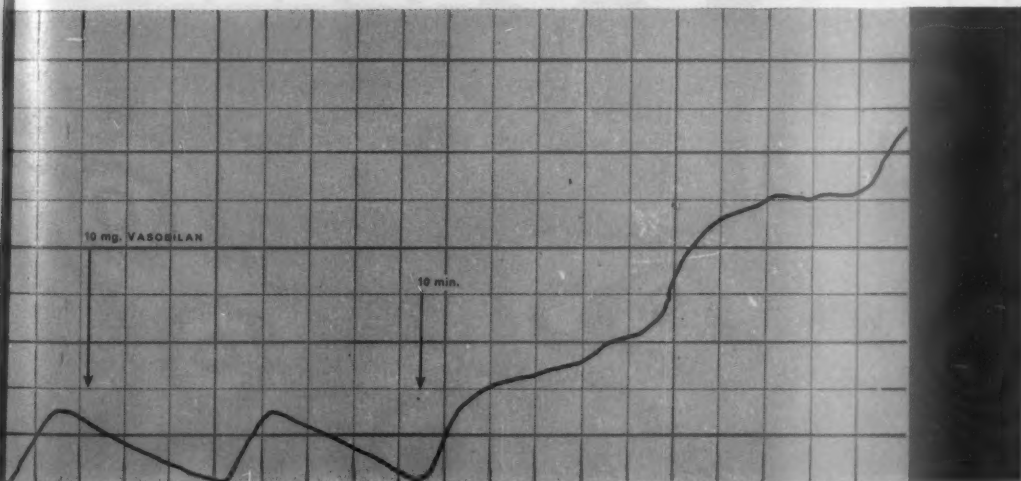
**without** development of tolerance<sup>1</sup>

**Availability:** VASODILAN Tablets, 10 mg., bottles of 100. VASODILAN Injection, Ampuls, 2 cc. (5 mg./cc.), boxes of 6.

**Oral Dosage:** 10 or 20 mg. (1 or 2 tablets) three or four times a day. For complete details on indications, dosage, administration and clinical background of VASODILAN, see the brochure on this product available on request from Mead Johnson and Company, Evansville 21, Indiana.

**References:** (1) Kaindi, F.; Samuels, S. S.; Selman, D., and Shaffel, H.: *Angiology* 10:185-192 (August) 1959. (2) Kaindi, F.; Pärtan, J., and Polsterer, P.: *Wien. klin. Wchnschr.* 69:180, 1959. (3) Brücke, F., et al.: *Wien. klin. Wchnschr.* 68:183, 1956. (4) Nash, C. B.; Drinnon, V., and Clark, B. B.; abstracted, *Fed. Proc.* 17:397 (March) 1958. (5) Singer, R.: *Wien. med. Wchnschr.* 107:734-736 (Sept.) 1957. (6) Dungan, K. W., and Lish, P. M.; abstracted, *Fed. Proc.* 17:365 (March) 1958. (7) Billiottet, J., and Ferrand, J.: *Semaine méd.* 34:635-637 (May) 1958.

Plethysmographic tracing of toe showing increase in blood flow starting 10 minutes after injection of 10 mg. of VASODILAN. Increased flow maintained for one hour. (Plethysmographic base line already established.) Courtesy S. S. Samuels, M. D., New York



**Mead Johnson**  
Symbol of service in medicine

gout

# ANTURAN<sup>TM</sup>

(sulfapyrazone GEIGY)

## High Potency Uricosuric Agent

By significantly increasing renal excretion of urate and thus lowering plasma uric acid, the new highly potent uricosuric agent ANTURAN strikes directly at the basic metabolic defect in gout.

Exceptionally high potency...4 to 6 times that of probenecid...is the outstanding characteristic of ANTURAN. The effectiveness of ANTURAN is retained indefinitely and tolerance to it is good.

## Clinically, ANTURAN:

- Prevents formation of new tophi
- Causes gradual absorption of old tophi
- Relieves chronic pain
- Restores joint mobility

ANTURAN is not designed for the treatment of acute attacks for which BUTAZOLIDIN is recommended. Detailed Information On Request

YU, T. F.; Burns, J. J., and Gutman, A. B. Arth. & Rheumat. 1:532, 1958.

ANTURAN (sulfapyrazone GEIGY). Scored tablets of 100 mg. in bottles of 100.

BUTAZOLIDIN (phenylbutazone GEIGY)

Geigy  
Ardley, New York  
1955



**WITH VESPRIN**  
Squibb triflupromazine hydrochloride

**STOP**  
**NAUSEA &  
VOMITING**

**Dosage:** Intravenous, 5 to 12 mg. / Intramuscular, 5 to 15 mg. / Oral prophylaxis, 20 to 30 mg. daily / **Supply:** Tablets, 10, 25, and 50 mg., bottles of 50 and 500 / Emulsion, 30-cc. dropper bottles and 120-cc. bottles (10 mg./cc.) / Parenteral Solution, 1-cc. multiple dose vial (20 mg./cc.) / 10-cc. multiple dose vial (10 mg./cc.) / Vesprin Injection Unimatic (15 mg. in 0.75 cc.)

**Vesprin**/the tranquilizer that fills a need in every major area of medical practice/ anxiety and tension states, pre- and postoperative tranquilization, alcoholism, and obstetrics.

**SQUIBB**



**Squibb Quality — the  
Priceless Ingredient**

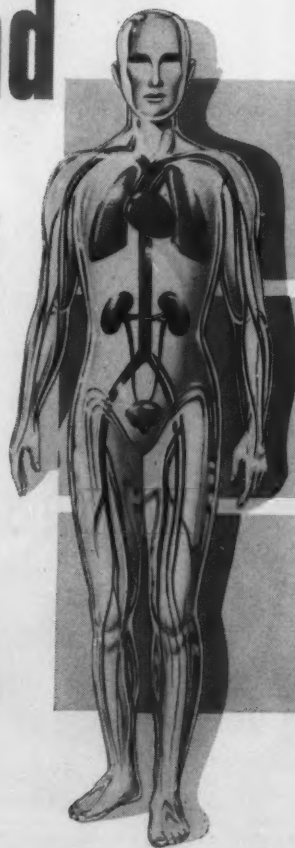
Please Mention this Journal when writing to Advertisers

**NEW**

# HYDRODIURIL<sup>TM</sup>

(HYDROCHLOROTHIAZIDE)

**simplifies\* and  
improves any  
regimen for  
hypertension**



*\*it's as easy as 1, 2, 3 to use*

# HYDRODIURIL<sup>TM</sup>

(HYDROCHLOROTHIAZIDE)

**1** Initiate therapy with HYDRODIURIL: one 25 mg. tablet or one 50 mg. tablet once or twice a day. HYDRODIURIL by itself often causes an adequate drop in blood pressure over a period of two to three weeks. This may be all the therapy some patients require.

**2** Add or adjust other agents as required: HYDRODIURIL enhances the activity of all commonly-used antihypertensive agents; thus, the dosage of other medication (rauwolfia, reserpine, hydralazine, veratrum) should be initiated or adjusted as indicated by patient condition. If a ganglion-blocking agent is contemplated or being used, usual dosage must be reduced by 50 per cent.

**3** Adjust dosage of all medication: the patient must be frequently observed and careful adjustment of all agents should be made to establish optimal maintenance dosage.


**Supplied:** 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) bottles of 100 and 1,000. Additional literature for the physician is available on request.

HYDRODIURIL is a trademark of Merck & Co., Inc. Trademarks outside the U. S.: DICHLOTIDE, DICLOTIDE, HYDROSALURIC.



MERCK · SHARP & DOHME, Division of Merck & Co., Inc., Philadelphia 1, Pa.

Please Mention this Journal when writing to Advertisers

now! a safe,   
new long-acting  
biologic stimulant:

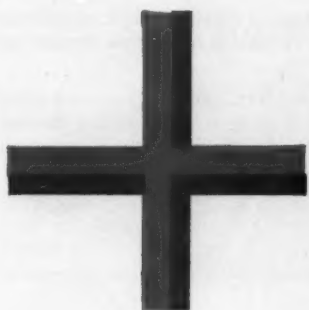
# Durabo

**DURABOLIN**, a totally new biologic stimulant, is the safest and most potent long-acting tissue-building agent now available to physicians. Clinical studies, conducted on a broad scale for more than three years in England, Canada, Europe and the United States, indicate clearly that **DURABOLIN** exerts its revitalizing effects without the drawbacks and dangers characteristic of tissue-building steroids. *Under the influence of DURABOLIN*, normal cell growth is stimulated, muscular tissue mass increased. Negative nitrogen balance rapidly becomes positive. Appetite improves dramatically. Weight gain occurs from increased solid tissue, without fluid retention. **DURABOLIN** therapy may also relieve pain in both pre-senile and senile osteoporosis, possibly by stimulating regenerative processes of bone.

**Given only once weekly** by bland, intramuscular injection, **DURABOLIN** produces a rapid, lasting sense of well-being, especially in the asthenic, undernourished or debilitated patient.

**DURABOLIN** is notably less costly than oral anabolic therapy, and produces no growth of facial hair or acne when administered in proper dosage. And thus far, after ten million injections, there has been no evidence of hepatic disorders or progestational effects.

**DURABOLIN** is supplied in 1-cc. ampuls and in 5-cc. vials, providing 25 mg. of nandrolone phenpropionate (**ORGANON**) per cc. of sesame oil. **Average adult dose:** 25 mg. (1 cc.) i.m. once weekly, or 50 mg. (2 cc.) i.m. every second week. Write for samples with complete literature and bibliography on **DURABOLIN**: Organon Inc., Orange, New Jersey.



**polin<sup>®</sup>**

Nandrolone phenpropionate injection, ORGANON

restores strength  
and vitality,  
builds working  
muscular weight,  
improves outlook  
and appetite

in:  
anorexia  
asthenia  
burns  
cachexia  
convalescence  
catabolic conditions  
debility states  
decubitus ulcers  
mammary cancer  
osteogenesis imperfecta  
osteoporosis  
pre- and post-surgery  
retarded growth  
uremia  
weight loss



Organon Inc. • Orange, N. J.

Please Mention this Journal when writing to Advertisers

# RONIACOL

FOR INTERMITTENT CLAUDICATION

...FOR PERIPHERAL VASOSPASM

**DIRECT VASCULAR RELAXATION.** RONIACOL relieves pain, extends range of walking and raises activity-tolerance by direct dilation of peripheral vessel musculature, thus increasing blood flow throughout the extremities.<sup>1-3</sup>

**NO KNOWN CONTRAINDICATIONS.** RONIACOL, unlike sympathetic blocking agents, may be used safely for prolonged periods in peripheral vasospasm of any etiology, even in patients with coronary disease. Further, RONIACOL (nicotinic alcohol) is converted at the cellular level to the pure vitamin (nicotinic acid); side effects are absent, negligible or inconsequential.<sup>1-4</sup>

References: (1) R. O. Gilhespy, *Brit. M. J.*, 1:207, 1957. (2) M. M. Fisher and H. E. Tebrock, *New York J. Med.*, 53:65, 1953. (3) C. M. Castro and L. de Soldati, *Angiology*, 4:165, 1953. (4) W. Redisch and O. Brandman, *Angiology*, 1:312, 1950. (5) G. Kagan, *Lancet* 2:53, 1959.

RONIACOL, scored 50-mg tablets, bottles of 100, 500, and 1000. RONIACOL ELIXIR, 50 mg of Ronicol per teaspoonful (5 cc), bottles of 16 oz and 1 gal.

RONIACOL®—brand of beta-pyridyl carbinol.

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, N. J.





*Now!*  
for the ambulatory patient, too —

Relief from the  
discomfort of  
flatulence due to  
intestinal atony

WARREN-TEED

# **ILOPAN<sup>®</sup>-CHOLINE** *tablets*

The successful use of parenteral ILOPAN, in thousands of hospitals, for prevention and relief of post-surgical retention of flatus and feces, has brought demands for similarly effective medication for ambulatory patients — those suffering from intestinal atonia and/or gas retention, as such or as complications of geriatric problems, gastric hyperacidity, gastritis, pregnancy, irritable colon, ureteroenterostomy, regional ileitis, splenic flexure syndrome, infectious hepatitis, cholecystitis.

To ILOPAN (brand of d-pantothenyl alcohol) which aids formation of coenzyme A (essential to acetylation of choline) has been added Choline, the parent substance of acetylcholine (necessary for gastrointestinal tonus). *Effectiveness? — 90% in three independent clinical evaluations of patients of all ages from 20 to 80! And safe.*

COMPOSITION: Each tablet contains Ilopan (brand of d-pantothenyl alcohol) 50 mg., choline bitartrate 25 mg.

INDICATIONS: Gas retention in the atonic gastrointestinal tract of ambulatory patients.

DOSAGE: Two tablets three times daily. Three tablets three times daily in severe cases.

HOW SUPPLIED: Bottles of 100 and 500.



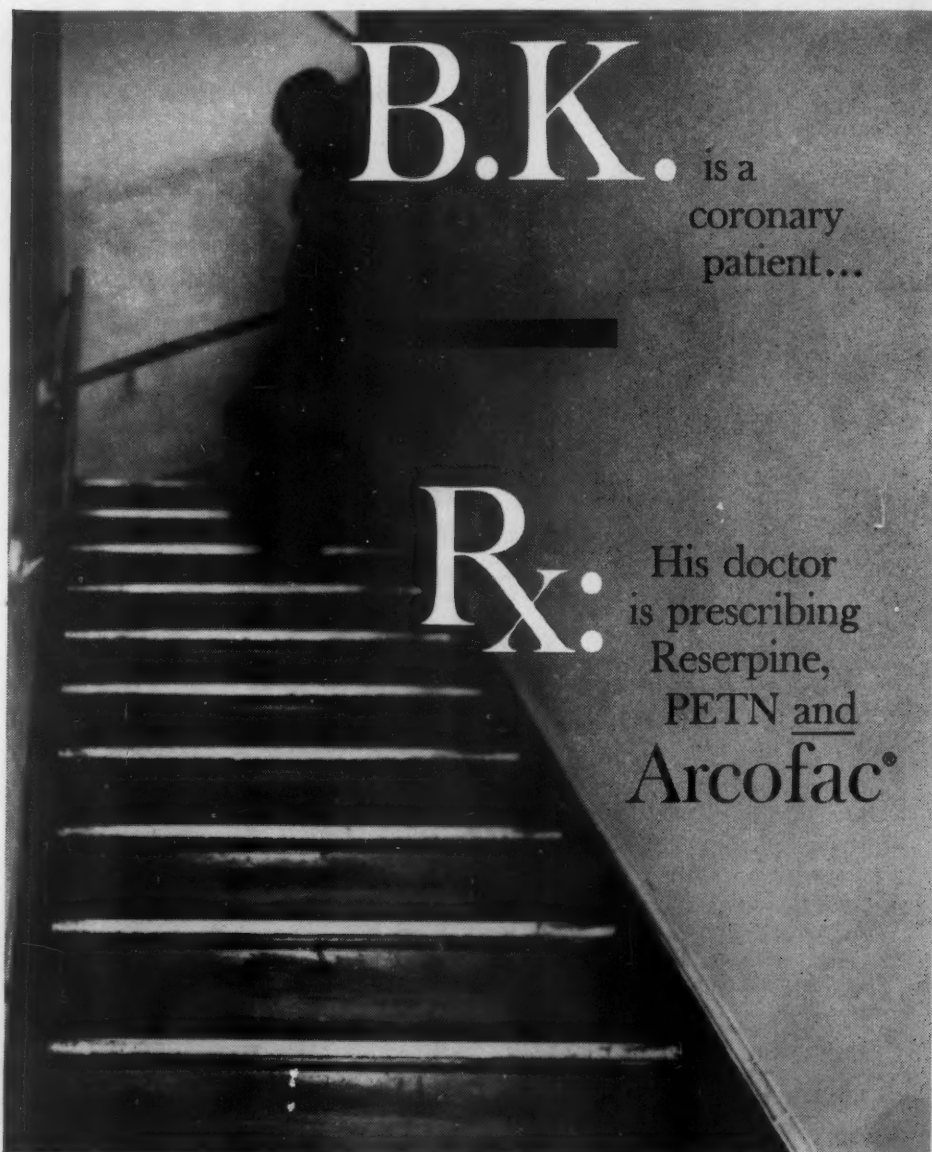
**THE WARREN-TEED PRODUCTS COMPANY**  
COLUMBUS 8, OHIO

Dallas

Chattanooga

Los Angeles

Portland



**B.K.** is a  
coronary  
patient...

**Rx:** His doctor  
is prescribing  
Reserpine,  
PETN and  
**Arcofac**®

Arcofac is an important additional safeguard to prevent  
or control hypercholesteremia in cardiac conditions

**EVERY PATIENT WITH CORONARY DISEASE DESERVES THE ADDITIONAL PROTECTION AFFORDED BY ARCOFAC**

Arcofac (Armour Cholesterol Lowering Factor) lowers elevated blood cholesterol levels, safely, effectively, and without imposing radical dietary changes.

Each tablespoonful (15 ml.) of Arcofac contains:  
Essential fatty acids\* . . . . . 6.8 Gm.  
(measured as linoleic) with 2.5 I. U. of Vitamin E†  
Pyridoxine hydrochloride (Vitamin B<sub>6</sub>) . . . 1.0 mg.

\*Supplied by safflower oil which contains the highest concentration of polyunsaturated fatty acids of any commercially available vegetable oil.

†Added as Mixed Tocopherols Concentrate, N.F.

ARMOUR PHARMACEUTICAL COMPANY  
KANKAKEE, ILLINOIS • *Armour Means Protection*



**Doctor: if you have  
low-salt patients you can  
take rigid diet plans  
(and all their bother)  
out of your treatment**



new—for edema and hypertension

**ORETIC™**

(HYDROCHLOROTHIAZIDE, ABBOTT)



Your most potent means when  
the end is saluretic\*



**put some real pleasure  
(and some real salt)  
back on their table**





new product  
for edema and  
hypertension

Doctor: if you have low-salt patients you can put some real pleasure (and some real salt) back on their table . . . take rigid diet plans (and all their bother) out of your treatment

**ORETIC<sup>TM</sup>**  
(HYDROCHLOROTHIAZIDE, ABBOTT)

your most potent means when the end is saluresis\*

In simplest terms, giving new **ORETIC** is like packaging a low-salt regimen in a single tablet . . . because **ORETIC** steps up excretion of sodium and chloride, and thereby often cuts down the need for an extremely rigid diet.

Further, it makes sense that the more potent the diuretic-antihypertensive, the greater the chances that rigid sodium restrictions can be relaxed.

And new **ORETIC** is the most potent, most effective oral diuretic-antihypertensive yet discovered. It has a high therapeutic ratio, low toxicity. It works successfully with dosages only 1/10-1/15 those of chlorothiazide.

\*In many clinical problems the elimination of salt (saluresis) is just as important as diuresis. And **Oretic** provides your most potent means to these ends.

If you have low-salt patients . . . patients with hypertension, renal edema, congestive heart failure, toxemia of pregnancy . . . consider **ORETIC**. Because if you adjust **ORETIC** dosage and sodium intake together, you may well find that you can put some real pleasure (and some real salt) back on the patient's table . . . and spend a lot less time and effort attending to details of rigid diet-planning.

New **ORETIC** is available for your trial in 25- and 50-mg. tablets, bottles of 100 and 1000.

Ask your Abbott Representative for a copy of the **ORETIC** PHYSICIAN'S LITERATURE containing complete indications, dosage and precautionary information.

**ORETIC**—THIRTY YEARS FOR HYPERTENSION AND EDEMA, ABBOTT





*relieves rigidity  
and reduces muscle spasm  
in the  
parkinson patient*

**PHENOXENE™**

a new synthetic compound

"Chlorphenoxamine (Phenoxene) exerts a gentle yet potent action . . . a muscle relaxant action also an energizing and stimulating action, without induction of excitement or agitation. Patients are able to move faster and more freely and with greater strength and longer endurance. It helps to loosen rigid muscles, and it successfully counteracts akinesia, tiredness, and weakness."\*

\*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. 170:37 (May 2) 1959.

A REPRINT OF THE COMPLETE ARTICLE AND CLINICAL TRIAL SUPPLIES ARE AVAILABLE ON REQUEST.



**PITMAN-MOORE COMPANY**

DIVISION OF ALLIED LABORATORIES, INC. • INDIANAPOLIS 6, INDIANA

**NOW**

*... a new way  
to relieve pain  
and stiffness  
in muscles  
and joints*

INDICATED IN:

MUSCLE STIFFNESS

LUMBOSACRAL STRAIN

SACROILIAC STRAIN

WHIPLASH INJURY

BURSITIS

SPRAINS

TENOSYNOVITIS

FIBROSITIS

FIBROMYOSITIS

LOW BACK PAIN

DISC SYNDROME

SPRAINED BACK

"TIGHT NECK"

TRAUMATIC STRAINS  
AND BRUISES

POSTOPERATIVE  
MYALGIA



- Exhibits unusual analgesic properties, different from those of any other drug
- Specific and superior in relief of **SOM**atic pain
- Modifies central perception of pain without abolishing natural defense reflexes
- Relaxes abnormal tension of skeletal muscle

# SOMA<sup>TM</sup>

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

- More specific than salicylates
- Less drastic than steroids
- More effective than muscle relaxants

**SOMA** has a unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. **SOMA** is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with **SOMA** than with any previously used analgesic, sedative or relaxant drug.

**SOMA** also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

**ACTS FAST.** Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

**NOTABLY SAFE.** Toxicity of **SOMA** is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

**EASY TO USE.** Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

**SUPPLIED:** Bottles of 50 white sugar-coated 350 mg. tablets.

*Literature and samples on request.*



**WALLACE LABORATORIES, NEW BRUNSWICK, N. J.**

now—  
**control**  
virtually  
all runaway  
diarrheas..  
promptly,  
effectively  
with

# Donnagel<sup>®</sup>

or Donnagel<sup>®</sup> with Neomycin

Prompt and more dependable control of virtually all diarrheas can be achieved with the comprehensive DONNAGEL formula, which provides adsorbent, demulcent, antispasmodic and sedative effects—with or without an antibiotic. Early re-establishment of normal bowel function is assured—for all ages, in all seasons.

**DONNAGEL: In each 30 cc. (1 fl. oz.):**

Kaolin (90 gr.).....	6.0 Gm.
Pectin (2 gr.).....	142.8 mg.
Hyoscyamine sulfate .....	0.1037 mg.
Atropine sulfate .....	0.0194 mg.
Hyoscine hydrobromide ...	0.0065 mg.
Phenobarbital (1/4 gr.).....	16.2 mg.

**DONNAGEL WITH NEOMYCIN**

Same formula, plus	
Neomycin sulfate .....	300 mg.
(Equal to neomycin base, 210 mg.)	

**A. H. ROBINS CO., INC., Richmond 20, Virginia** • Ethical Pharmaceuticals of Merit since 1878

## REFLECTION ON CORTICOTHERAPY:



Particularly in corticotherapy, the intent is not to treat diseases, but to treat patients. This intent is best served by using the steroid that has the best ratio of desired effects to undesired effects:

the corticosteroid that hits the disease, but spares the patient

# Medrol<sup>\*</sup>

**Upjohn**THE UPJOHN COMPANY  
KALAMAZOO, MICHIGAN\*TRADEMARK, REG. U. S. PAT. OFF. — METHYLPREDNISOLONE, UPJOHN

Please Mention this Journal when writing to Advertisers

Overwhelming evidence<sup>1-13</sup> proves:

# HIGH- DOSAGE NICOTINIC ACID EFFECTIVELY LOWERS CHOLESTEROL LEVELS WITHOUT DIETARY RESTRICTIONS<sup>1,2</sup>

## VASTRAN FORTÉ<sup>®</sup>

capsules

In a recent report<sup>1</sup> on 44 patients, VASTRAN FORTÉ reduced plasma cholesterol levels to normal in 21 patients and lowered cholesterol levels by at least 40% in 14 more patients during a 30-week period. *There was no change in diet.*

VASTRAN FORTÉ produces no significant side effects on long-term administration. "No toxic reactions have been found by clinical and laboratory observations, including a battery of seven tests of hepatic function and needle biopsies of the liver in 17 patients after one year of therapy."<sup>1</sup> However, patients must be told to expect pronounced warm flushing within approximately 15 minutes of the early doses. This effect is the normal initial response to high-dosage nicotinic acid, and is in no way harmful. It generally does not occur after one or two weeks.

VASTRAN FORTÉ contains anticholesterol dosage of nicotinic acid<sup>1-13</sup> fortified by added B-complex factors to guard against vitamin deficiencies due to large dosage of a single B factor;<sup>14-15</sup> plus pyridoxine to improve utilization of unsaturated fatty acids in normal diets<sup>16-17</sup> and ascorbic acid<sup>18</sup> for support against degenerative arterial changes.

Each VASTRAN FORTÉ Capsule contains: nicotinic acid, 375.0 mg.; ascorbic acid, 50.0 mg.; riboflavin, 2.5 mg.; thiamine mononitrate, 5.0 mg.; pyridoxine hydrochloride, 0.5 mg.; calcium pantothenate, 2.5 mg.; cobalamin concentrate (vitamin B<sub>12</sub> activity), 10.0 mcg. Dosage: Initial Dosage—2 capsules four times a day after meals for twelve weeks. Thereafter dosage should be adjusted according to response. Maintenance requirements may vary from 1 capsule q.i.d. to 4 capsules q.i.d. Supply: Bottles of 100.

WAMPOLE LABORATORIES, STAMFORD, CONNECTICUT

**Bibliography:** 1. Parsons, W. B., Jr., and Flinn, J. H.: A.M.A. Arch. Int. Med. 103:783, 1959. 2. Parsons, W. B., Jr., and Flinn, J. H.: J.A.M.A. 165:234 (Sept. 21) 1957. 3. O'Reilly, P. O.: Canad. M. A. J. 78:402 (March 15) 1958. 4. Altschul, R., and Hoffer, A.: Arch. Biochem. 73:420, 1958. 5. Achon, R. W. P.; Berge, K. G.; Barker, N. W., and McKenzie, R. E.: Circulation 17:497, 1958. 6. Altschul, R., and Hoffer, A.: Circulation 16:499, 1957. 7. Hoffer, A., and Calbeck, M. J.: J. Ment. Sc. 103:810, 1957. 8. Parsons, W. B., Jr., and Flinn, J. H.: Circulation 16:499, 1957. 9. Achon, R. W. P.; Berge, K. G.; Barker, N. W., and McKenzie, R. E.: Circulation 16:499, 1957. 10. O'Reilly, P. O.; Demay, M., and Kotowski, K.: Arch. Int. Med. 100:797, 1957. 11. deSoldati, L.; Stritzler, G., and Balassanian, S.: Prensa méd. argent. 44:3286 (Nov. 8) 1957. 12. Parsons, W. B., Jr., et al.: Proc. Staff Meet. Mayo Clin. 31:377 (June 27) 1956. 13. Altschul, R.; Hoffer, A., and Stephen, J. D.: Arch. Biochem. 54:588, 1955. 14. Seebrell, W. H., and Harris, R. S.: The Vitamins: Chemistry, Physiology, Pathology, New York, Academic Press, 1954, vol. 2, p. 551. 15. Gregory, I.: J. Ment. Sc. 101:85, 1955. 16. Sinclair, H. M.: Lancet 1:381, 1956. 17. Page, I. H., et al.: J.A.M.A. 164:2048 (Aug. 31) 1957. 18. Rosenfeld, L.: Am. J. Clin. Nutrition 5:286, 1957.

## PROTECTS AGAINST ANGINAL ATTACKS

RUSSEK: PETN is "... the most effective drug currently available for prolonged prophylactic treatment of angina pectoris."<sup>1</sup> Prevents some 80% of anginal attacks.

## EASES CARDIAC TENSION

RUSSEK: "I favor ATARAX [as the tranquilizer for the anxious cardiac]...because there is an absence of side effects with this drug, and also because in cardiacs who are troubled with ectopic beats, ATARAX has a quinidine-like action."<sup>2</sup>

# PETN + ATARAX<sup>®</sup>

(Contains 10 mg. PETN + 10 mg. ATARAX)

(PETN + ATARAX)

# CARTRAX<sup>®</sup>

**Dosage:** Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX).

For convenience, write "CARTRAX 10" or "CARTRAX 20."

**Supplied:** In bottles of 100.

**References:** 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.



New York 17, N. Y.  
Division, Chas. Pfizer & Co., Inc.  
Science for the World's Well-Being



NOW...

in bronchial asthma

# PREDNAMIN<sup>TM</sup> tablets

"potentiated prednisone"

*breaks the  
"side-effects barrier"  
to full, long-range  
corticosteroid benefits*

PREDNAMIN brought excellent or good relief to 76% of 50 asthmatic patients . . . all of whom had responded unsatisfactorily to one or more years of specific therapy and to epinephrine, ephedrine and aminophylline. Although treatment was prolonged and continuous, only 2 patients required withdrawal of PREDNAMIN because of side effects.\*

The optimally balanced PREDNAMIN combination magnifies the efficacy of small doses of prednisone . . . but leaves corticosteroid hazards at a low-dose minimum. With PREDNAMIN, problem asthmatics and patients with atopic and contact dermatoses need no longer be deprived of continuing and often dramatic corticosteroid benefits.

Each PREDNAMIN Tablet contains prednisone 2.5 mg., chlorphenpyridamine maleate 2.0 mg., and ascorbic acid 250.0 mg. Bottles of 30 and 100.

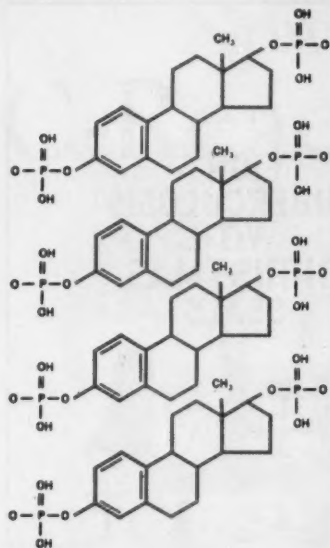
\*Swartz, H.: To be published.



**DOME CHEMICALS INC.**

New York • Los Angeles • Montreal

World Leader in Dermatologicals



acts as a  
synthetic  
gland  
secreting  
natural  
estrogen...

# "ESTRADURIN"®

BRAND OF POLYESTRADIOL PHOSPHATE

## SPECIFICALLY RECOMMENDED IN PROSTATIC CARCINOMA

"ESTRADURIN" simulates the physiologic release of estrogen. Biologically active units of estradiol are slowly split off from the parent molecule, and free estradiol is metabolized in the same manner as the endogenous hormone.

**Long acting without depot effect at site of injection.** Within 24 hours, 90 per cent of the total dose disappears from the injection site. Clearance from the blood stream is rapid, and within 48 hours varying amounts appear in the reticuloendothelial cells where storage is apparently passive. As the amount of circulating polyestradiol phosphate falls below a certain level in the body, more passes from the reticuloendothelial system assuring relatively constant levels in the blood stream.

**Proved Clinically** — In a composite study of 110 cases of prostatic carcinoma treated with "ESTRADURIN," improvement occurred in 93 per cent of the entire group in the following order of frequency:<sup>1</sup> greater sense of well-being . . . better appetite . . . weight gain . . . palpable changes in prostate . . . reduction in pain . . . reduction of edema in extremities . . . improved cardiac status . . . disappearance of diarrhea. Conspicuously absent have been reports of edema, nausea, and vomiting.

**Simplified Dosage**/Intramuscular injection of 40 to 80 mg. every two to four weeks or less frequently, depending on response of the patient.

**Availability**/No. 451/Each package contains: One "Secule"® containing 40 mg. of polyestradiol phosphate and one 2 cc. ampul of sterile diluent.

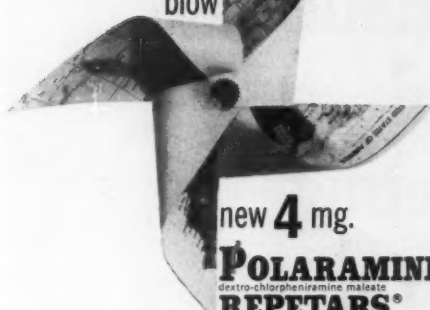


**Ayerst Laboratories**

New York 16, N. Y. • Montreal, Canada

1. Goodhope, C. D.: Paper and Scientific Exhibit presented before the Western Section of the American Urological Association, May 27-30, 1957, Seattle, Washington.  
Bibliography and literature on request. 5915

wherever  
the 4  
winds  
blow



new 4 mg.

**POLARAMINE®**  
dextro-chlorpheniramine maleate  
**REPETABS®**

for prophylaxis and relief  
of allergic reactions



Symbol of  
the one-dose  
convenience  
you want for  
your patient

SCHERING CORPORATION  
Bloomfield, New Jersey

*Schering*

EN-1485-9

**FIGHT  
TUBERCULOSIS  
WITH  
CHRISTMAS  
SEALS**



## IMPORTANT NEW PSYCHOACTIVE AGENT

IN DEPRESSED PATIENTS, treatment with CATRON<sup>®</sup> elevates mood, diminishes apathy and social withdrawal, increases alertness and confidence. Efficacy reported comparable to electroshock in endogenous depressions and superior to it in reactive depressions.

# Catron<sup>®</sup>



β-phenylisopropyl hydrazine supplied as the hydrochloride

For complete information send for Brochure No. 19, CATRON



LAKESIDE LABORATORIES, INC.  
MILWAUKEE 1, WISCONSIN

50559

Now  
**C-Reactive Protein**  
test results  
in **2 minutes**  
by this new  
easy-to-read slide method

**SCREENING TEST**

Mix one drop of serum specimen with two drops of CR-TEST reagent on glass slide.

Presence of C-reactive protein will be indicated within one to two minutes by *easily visible* flocculation.

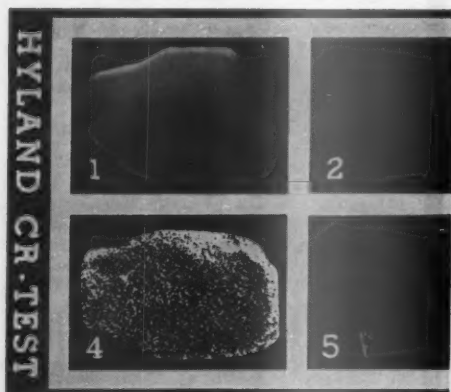
**QUANTITATIVE TEST**

Levels of C-reactive protein are equally easy to determine. Prepare serum dilutions of test specimen in buffered diluent. On successive sections of glass slide, mix one drop of CR-TEST reagent with one drop of each serum dilution. The highest dilution showing visible flocculation within two minutes is taken as the C-reactive protein titer of the specimen.

**SUPPLIED**

Kits containing Latex-Anti-C-Reactive Protein Reagent, Glycine-Saline Buffer Diluent for serum dilution, capillary pipettes for serum transfer, and 2 divided glass slides. Each kit sufficient for 60 screening tests. \$10.00 per kit.

Also available: CR-TEST Positive Control Serum, 0.5 cc.



Hyland  
**CR-TEST\***

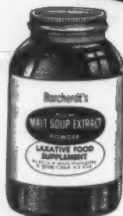
**HYLAND LABORATORIES**

4501 Colorado Blvd., Los Angeles 39, Calif.  
160 Lockwood Ave., Yonkers, N.Y.

\*Trade Mark of Hyland Laboratories

**for**  
**GERIATRIC**  
**CONSTIPATION**

**Borcherdt's**  
**MALT SOUP EXTRACT**  
(MALTSUPEX)  
**POWDER**



**is**  
**Gentle,**  
**Safe,**  
**Sure,**  
**Dietary.**

It's available in two forms, liquid and powder, but most adults prefer the mild tasting powder. It dissolves instantly in milk, water or juices. It promotes aciduric flora in the lower bowel which helps restore normal function. Long term treatment produces no side effects. Diabetic patients should allow for 60 calories for each tablespoonful.

Hootnick<sup>(1)</sup> reports, "Stools became soft in all patients and, within one week, bowel evacuations were accomplished with ease. Most patients liked the taste of the product, and the majority of them reported a feeling of well-being."

Cass and Frederik<sup>(2)</sup> also found that "Malt Soup Extract produced soft, easily evacuated stools without any side effects in constipated elderly patients."

Marshall<sup>(3)</sup> found it "a simple but highly effective treatment for chronic constipation in patients of all ages."

**Dose:** 2 tablespoonfuls twice a day. Available, liquid and powder, 8 ounce and 16 ounce bottles, at pharmacies.

**Send for clinical samples**

(1) Hootnick, H. L.: Jnl. Amer. Ger. Soc., 4:1021-1030, 1956. (2) Cass, L. J. and Frederik, W. S.: Jnl. Lancet, 73: 414-416, 1953. (3) Marshall, W.: So. Dak. J. Med. & Pharm. 8:151-153, 1955.

**Borcherdt Company**

217 North Wolcott Avenue, Chicago 12, Illinois  
In Canada: Chemo-Drug Co., Ltd., Toronto, Ont.

**Borcherdt Company** **GP**  
217 N. Wolcott Ave., Chicago 12, Ill.  
Gentlemen: Please send samples and literature of your Malt Soup Extract (Maltsupex)

☐ Powder ☐ Liquid

M.D.

Address \_\_\_\_\_

City \_\_\_\_\_ Zone \_\_\_\_\_ State \_\_\_\_\_

**ANNOUNCING**

**A NEW LAMOTTE OUTFIT for RAPID**  
**DETERMINATION OF CALCIUM IN**  
**BLOOD and URINE**

Results on blood or urine in less than 10 minutes. Employs the method of Myers and Raydel, based on the direct titration of Calcium with EDTA, using a new, two tube, titration employing fluorescent screen as a titrating background.

This method is simple, rapid, and accurate. The results on blood serum are accurate to 0.3 mg. per 100 ml. serum, which compares favorably with the most accurate standard laboratory methods.

The LaMotte Complexometric Calcium Analysis Outfit is recommended for both Office and Laboratory tests.

*Information on request*

**LaMOTTE CHEMICAL**  
**PRODUCTS COMPANY**

Dept. IM, Chestertown, Md., U.S.A.

**PROFESSIONAL CARE AND**  
**TRAINING FOR THE**  
**MENTALLY RETARDED**

The Training School at Vineland, New Jersey is especially equipped for the care and treatment of mentally retarded children. Boys and girls two years of age and up with a mental potential of six years are accepted. They receive individual care and treatment. They live in small groups in attractive cottages. They work and play with children at their own level. They are helped to develop to their full potential.

The carefully selected medical, dental, psychiatric, psychological, physiological staff administer six comprehensive programs:

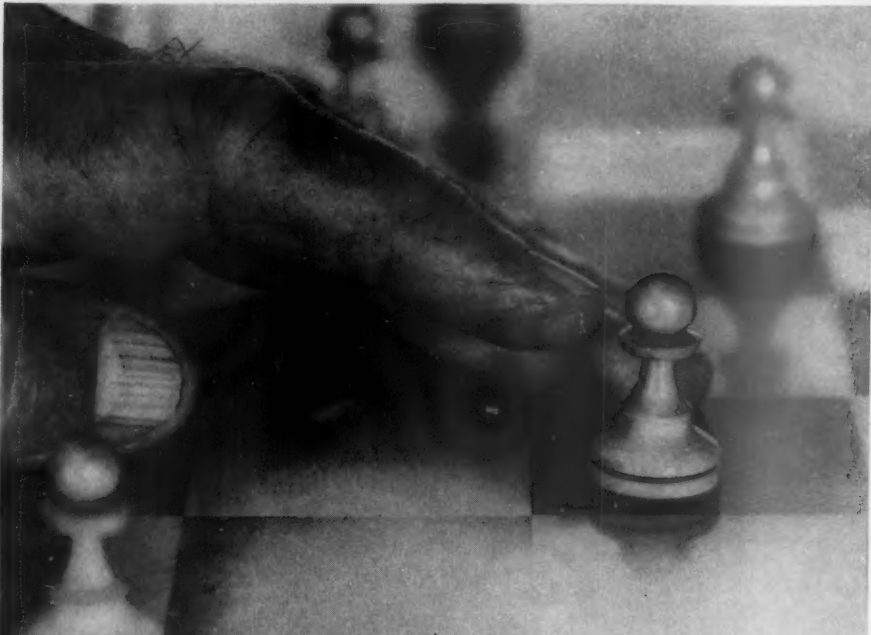
- Observation & Diagnosis
- Education & Training
- Custodial Care
- Residential Supervision
- Summer Program
- Psychiatric Treatment Center

500 children can be accommodated on the beautiful 1600-acre estate located in southern New Jersey near the seashore. The Training School Research Laboratory has been famed for continuous study of causes, prevention and treatment of mental retardation since 1888. For information write: Registrar, Box 1.

**THE TRAINING SCHOOL**  
**AT VINELAND, NEW JERSEY**

*A private non-profit residential center for the care and treatment of the mentally retarded*

Please Mention this Journal when writing to Advertisers



## fingertip control

**IN PARKINSONISM**, improved functional capacity is the therapeutic goal. Studies show that Parsidol permits greater freedom of movement, helps control tremor and muscular rigidity.<sup>1,2</sup> Even self-care activities, formerly most difficult, are made easier with Parsidol.<sup>2</sup>

Parsidol exercises a mood-lifting effect in the patient at the same time that his physical coordination and dexterity return. Though effective by itself, Parsidol is also compatible with most other anti-parkinsonian drugs. Side effects are minimal. Most patients respond to a maintenance dosage of 50 mg. q.i.d.

1. Doshay, L. J. et al. *J.A.M.A.* 160:348 (Feb.) 1956.

2. Berris, H.: *T. Lancet* 74:245 (July) 1954.

# PARSIDOL®

brand of ethopropazine hydrochloride



**Now**

*in inflammatory anorectal disorders . . .*

## The Promise of Greater Relief

the first suppository to contain

hydrocortisone for effective control of proctitis

- Proctitis accompanying ulcerative colitis
- Radiation proctitis
- Postoperative scar tissue with inflammatory reaction
- Acute and chronic nonspecific proctitis
- Acute internal hemorrhoids
- Medication proctitis
- Cryptitis



**Ulcerative Colitis**



**Radiation Proctitis**



**Postoperative  
Scar Tissue**

Supplied: Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.


# Wyanooids<sup>®</sup> HC

*Rectal Suppositories with Hydrocortisone, Wyeth*



Philadelphia 1, Pa.

"'JUST A LITTLE CASE OF CYSTITIS'..."



for Certainty  
against the Cocci

**Erythrocin**  
(Erythromycin, Abbott)

*an uncommon antibiotic for common infections*

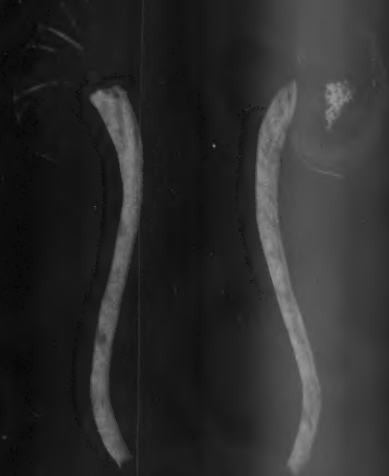
Provides fast, high blood and tissue concentrations—plus an unparalleled safety record. Erythrocin is available in easy-to-swallow Filmtabs® (100 and 250 mg.); in tasty, citrus-flavored Oral Suspension (200 mg. per 5-cc. teaspoonful); and for intravenous and intramuscular use.



®FILMTABS—FILM-SEALED TABLETS, ABBOTT; U.S. PAT. NO. 2,881,098

900139

“‘Just a little case of cystitis’ may actually have already involved the kidney parenchyma before the bladder became infected.”<sup>1</sup>



“The first evidence of inflammatory disease of kidney or prostate often is vesical irritability.”<sup>2</sup>

WHEN THE SYMPTOMS OF CYSTITIS

# FURADANTIN<sup>®</sup>

(brand of nitrofurantoin)

for rapid control of infection throughout the G. U. system

Rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria including organisms such as staphylococci, Proteus and certain strains of Pseudomonas, resistant to other agents

- actively excreted by the tubule cells in addition to glomerular filtration
- negligible development of bacterial resistance after 7 years of extensive clinical use
- excellent tolerance—nontoxic to kidneys, liver and blood-forming organs
- safe for long-term administration

AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. q.i.d. with meals and with food or milk on retiring. Supplied: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Editorial J.M.A. Georgia 46:433, 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953, p. 330.

NITROFURANS—a unique class of antimicrobials—neither antibiotics nor sulfonamides  
EATON LABORATORIES, NORWICH, NEW YORK

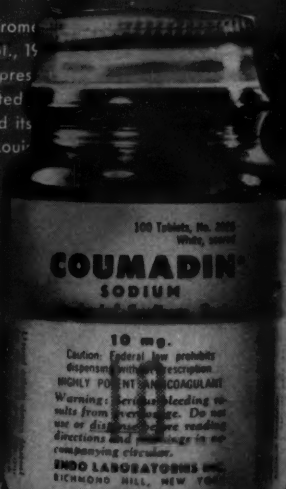
# COUMADIN BIBLIOGRAPHY

## Published studies on anticoagulant therapy with COUMADIN

1. Friedman, B.: The use of anticoagulants in the treatment of coronary and cerebral vascular disease, *J. Tennessee M. A.* 52:171, May, 1959. 2. Shapiro, S.: Long term therapy of coronary arteriosclerosis, *Angiology* 10:126, Apr., 1959. 3. Vastola, E. F., and Frugh, A.: Anticoagulants for occlusive cerebrovascular lesions, *Neurology* 9:143, Mar., 1959. 4. Toohey, M.: Clinical experience with warfarin sodium, *Brit. M. J.* 2:892, Oct. 11, 1958. 5. Porter, R. R.; Richardson, D., and Mauck, H. P., Jr.: Clinical experiences with the anticoagulant warfarin sodium ("Coumadin Sodium"), *Virginia M. Month.* 85:465, Sept., 1958. 6. Trumble, E. A.: Clinical experience with intramuscular warfarin sodium (Coumadin Sodium), *Surg. Gynec. & Obst.* 107:303, Sept., 1958. 7. Goodman, D. H.: Early clue to visceral carcinoma—hemorrhage after intravenously given warfarin, *J.A.M.A.* 166:1037, Mar. 1, 1958. 8. Shapiro, C. M.; Lisker, R.; Lichtman, A. M., and Josephson, A. M.: Comparative clinical study of Coumadin Sodium and Dicumarol in patients with thromboembolic diseases, *Am. Heart J.* 55:66, Jan., 1958. 9. Yarrow, M. W.; Baer, S.; Kravitz, C., and Markson, V.: A preliminary report on sodium warfarin (Coumadin), *J. Albert Einstein M. Center* 5:205, June, 1957. 10. Baer, S.; Yarrow, M. W.; Kravitz, C., and Markson, V.: Clinical experiences with warfarin (Coumadin) sodium as an anticoagulant, *J.A.M.A.* 167:704, June 7, 1958. 11. Fremont, R. E., and Jagendorf, B.: Clinical observations on use of warfarin (Coumadin) sodium, a new anticoagulant, *J.A.M.A.* 165:1381, Nov. 16, 1957. 12. Shapiro, S., and Ciferri, F. E.: Intramuscular administration of the anticoagulant warfarin (Coumadin) sodium, *J.A.M.A.* 165:1377, Nov. 16, 1957. 13. Nicholson, J. H.: Clinical experiences with anticoagulants: A comparison of Coumadin (warfarin) Sodium and Dicumarol (bishydroxycoumarin), *Angiology* 8:456, Oct., 1957. 14. Kerrin, H. F.; Guidot, J., and Wilhelm, S. K.: Clinical experiences with the anticoagulant Coumadin (warfarin) Sodium, *Angiology* 8:302, June, 1957. 15. Goodman, D. H.: Experience with a new anticoagulant Coumadin\* (warfarin) Sodium, *Arizona Med.* 13:389, Oct., 1956. 16. Nicholson, J. H., and Leavitt, T.: Coumadin (warfarin) Sodium: A new anticoagulant, *New England J. Med.* 255:491, Sept. 13, 1956. 17. Clatanoff, D. V., and Meyer, O. O.: Further observations on use of warfarin sodium in anticoagulant therapy, *A.M.A. Arch. Int. Med.* 97:753, June, 1956. 18. Freeman, D. J., and Meyer, O. O.: Rectal administration of warfarin (Coumadin) sodium. Sodium [3 (2-acetylbenzyl)-4-hydroxycoumarin], *Proc. Soc. Exper. Biol. & Med.* 92:52, May, 1956. 19. Pollock, B. E.: Clinical experience with Coumadin Sodium, a new anticoagulant drug, *Angiology* 6:506, Dec., 1955. 20. Pollock, B. E.: Clinical experience with warfarin (Coumadin) sodium, a new anticoagulant, *J.A.M.A.* 159:1094, Nov. 12, 1955. 21. Shapiro, S.: The hypoprothrombinemia-inducing activity of warfarin sodium (Coumadin\* Sodium), *J. Kansas M. Soc.* 55:687, Dec., 1954. 22. Clatanoff, D. V.; Triggs, P. O., and Meyer, O. O.: Clinical experience with coumarin anticoagulants warfarin and warfarin sodium, *A.M.A. Arch. Int. Med.* 94:213, Aug., 1954. 23. Shapiro, S.: Warfarin sodium derivative: (Coumadin\* Sodium): An intravenous hypoprothrombinemia-inducing agent, *Angiology* 4:380, Aug., 1953.

## Other published literature referring to Endo's COUMADIN

24. Escudero, J.; McDevitt, E., and Wright, I. S.: Dicumarol, Coumadin, Marcumar and Tromexin: their action on the clot as registered by the thrombelastogram, *Circulation* 20:401, Sept., 1959. 25. Little strokes, *West Virginia M. J.* 55:259, Aug., 1959. 26. Wright, I. S.: Strokes: the present treatment, *Postgrad. Med.* 25:549, May, 1959. 27. Little, J. R.: Purpura fulminans treated with Coumadin, *J.A.M.A.* 169:104, Jan. 3, 1959. 28. Link, K. P.: The discovery of Dicumarol and its use, *Jan., 1959*. 29. Kleiner, I. S., and Orten, J. M.: *Human Biochemistry*, ed. 5, Mosby, St. Louis, 1958. 30. Meyer, O. O.: Use of anticoagulants in the treatment of coronary artery disease, *Postgrad. Med.* 24:110, Aug., 1958. 31. Toohey, M.: Long-term anticoagulant therapy for coronary artery disease, *Postgrad. Med.* 24:110, Aug., 1958. 32. McDevitt, E.; Wright, I. S., and Foley, W. T.: Present status cerebral vascular lesions, *M. Clin. North America*, May, 1958, p. 587. 33. Barker, N. V.: Anticoagulant therapy, *Minnesota Med.* 41:252, Apr., 1958. 34. Grant, W. C., and MacMillan, R.: Anticoagulant therapy, *Canad. M. A. J.* 78:317, Mar., 1958. 35. Current Therapy: Treatment of myocardial infarction, *Dis. Chest* 33:315, Mar., 1958. 36. Bratman, I.: Anticoagulants in myocardial infarction, *Feb., 1958*. 37. Toohey, M.: Anticoagulants in myocardial infarction, *Brit. M. J.* 1:22, Jan., 1958. 38. Warfarin, *Virginia M. Month.* 85:37, Jan., 1958. 39. Friedberg, C. K.: Recent advances in the management of myocardial infarction, *New York J. Med.* 57:3643, Nov. 15, 1957. 40. Abstract: Warfarin sodium, *M. Science* 2:62, Sept. 10, 1957. 41. Olwin, J. H., and Oglesby, P.: Long term anticoagulant therapy, *Obst. & Gynec.* 10:561, July, 1957. 42. Ware, A. G., and Stragnell, R.: Anticoagulant therapy: occurring pitfalls, *Ann. Int. Med.* 46:450, Mar., 1957. 43. Briner, D. H.: A study of 235 cases of myocardial infarction, *J. Am. Osteopath. A.* 56:349, Feb., 1957. 44. Cosgriff, S. W.: Anticoagulant therapy in myocardial infarction, *J. Chron. Dis.* 4:402, Oct., 1956. 45. Skillecorn, S. A., and Aird, R. B.: *M. Clin. North America*, May, 1958, p. 587. 46. Pollock, B. E.: The early management of myocardial infarction, *J.A.M.A.* 161:404, June 2, 1956. 47. Shapiro, S.: Anticoagulant therapy, *Surg. Clin. North America*, Apr., 1956, p. 469. 48. Wright, I. S.: Present status of anticoagulant therapy in the treatment of myocardial infarction; the use and misuse of anticoagulants; an evaluation of new anticoagulants, their indications and dosage, *Ann. Int. Med.* 43:942, Nov., 1955. 49. Shapiro, S. (editorial): The administration of the hypoprothrombinemia-inducing drugs, *Angiology* 6:498, Oct., 1955. 50. Olwin, J. H.: Principles of anticoagulant therapy and their application, *M. Clin. North America*, Jan., 1955, p. 227. 51. Shapiro, S., and Spitzer, J. M.: The use of Cepevit\* (ascorbic acid plus "P" factors) in drug-induced hypoprothrombinemia, *Angiology* 5:64, Apr., 1954.



Coumadin is the original  
and only warfarin sodium  
responsible for  
establishing this drug as  
"the best anticoagulant  
available today"<sup>30</sup>

*(over 50 published papers since 1953)*

# COUMADIN<sup>®</sup>

FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

## SODIUM

IN MYOCARDIAL INFARCTION  
AND OTHER THROMBOEMBOLIC DISORDERS

#### **TABLETS**

*For oral administration*—2 mg., lavender, scored; 5 mg., peach, scored; 10 mg., white, scored; 25 mg., red, scored.

#### **INJECTION**

*For parenteral administration*—Single Injection Units, consisting of one vial, 75 mg., and one 3-cc. ampul Water for Injection.

#### **AVERAGE DOSE**

*Initial*, 50 mg. *Maintenance*, 5-10 mg. daily, as indicated by prothrombin time determinations.

COUMADIN (warfarin) Sodium is manufactured under license from the Wisconsin Alumni Research Foundation... clinically established by Endo.

Complete Information and Reprints on Request

**ENDO LABORATORIES** Richmond Hill 18, New York

# SUSTAGEN<sup>®</sup>

Complete therapeutic nutriment  
POWDER

anorectic cycle—by reversing the malnutrition that perpetuates and intensifies it.

Sustagen restores appetite physiologically. Restores good nutrition with its high-calorie formula. Contains generous amounts of protein, vitamins, calcium, iron and other essential minerals...to help rebuild and repair tissue, re-establish nitrogen balance, provide quick energy, speed recovery and promote well-being. Easy to give by mouth or tube, Sustagen is well tolerated in severe or moderate malnutrition, in patients of all ages.

\*Elman, R.: GP 17:115-122 (March) 1958.

"Primary anorexia leads to a reduced intake that in turn provokes malnutrition that, curiously enough, increases anorexia."\*

Sustagen, a therapeutic food—complete in all known essential nutrients—breaks the



Mead Johnson

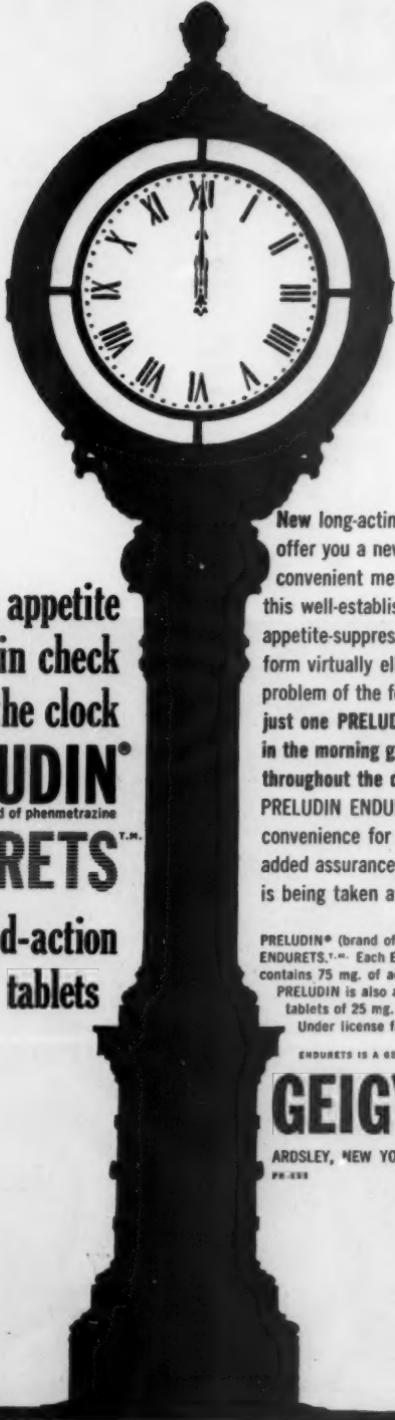
*Symbol of service in medicine*

EVANSVILLE, INDIANA

DAISY

break  
the  
anorectic  
cycle





keeping appetite  
in check  
around the clock  
**PRELUDIN®**  
brand of phenmetrazine  
**ENDURETS™**  
prolonged-action  
tablets

New long-acting PRELUDIN ENDURETS offer you a new method... a more convenient method... of administering this well-established, reliable appetite-suppressant. The new ENDURETS form virtually eliminates the vexing problem of the forgotten dose because... just one PRELUDIN ENDURET taken in the morning generally curbs the appetite throughout the day.

PRELUDIN ENDURETS afford greater convenience for your patient... added assurance to you that medication is being taken as prescribed.

PRELUDIN® (brand of phenmetrazine hydrochloride) ENDURETS™. Each ENDURETS prolonged-action tablet contains 75 mg. of active principle.

PRELUDIN is also available as scored, square pink tablets of 25 mg. for 2 to 3 times daily administration. Under license from C. H. Boehringer Sohn, Ingelheim.

ENDURETS IS A GEIGY TRADEMARK.

**GEIGY**

ARDSLEY, NEW YORK

PR-303



**common denominator: a.p.** People worlds apart—plumber, pediatrician, clubwoman, counterman—have one thing in common: angina pectoris. On “basic therapy” of Peritrate 20 mg. q.i.d. all remain normally active with fewer, less severe attacks, increased exercise tolerance, and reduced nitroglycerin dependence.

At times, however, personality problems, underlying apprehensions, emergency situations, or unpredictable schedules call for “basic therapy” plus individualized treatment. Broad coverage protection for each patient is afforded by Peritrate formulations in terms of Adaptable Prophylaxis:

Peritrate 20 mg., q.i.d. .... “basic therapy”  
 Peritrate with Phenobarbital, q.i.d. .... for the apprehensive patient  
 Peritrate with Aminophylline, q.i.d. .... for congestive failure  
 Peritrate Sustained Action, b.i.d. .... for convenient 24-hour protection  
 Peritrate with Nitroglycerin, p.r.n. .... to relieve the acute attack

## to increase coronary circulation in angina pectoris & postcoronary convalescence:

After a coronary, aiding the development of collateral circulation serves to reduce effects of myocardial damage and prevent ensuing anginal episodes. Peritrate, a selective long-acting vasodilator, may prove to be the drug of choice because it increases coronary flow without a significant fall in blood pressure.

A clinical supply of Peritrate 20 mg. is available from Dept. A. W.: Warner-Chilcott, Morris Plains, N. J.



MORRIS PLAINS, N.J.

# Peritrate®

brand of pentaerythritol tetranitrate

You can  
expect  
your  
patients  
with  
dysmenorrhea  
to return  
to normal  
activity  
when you  
prescribe

THE FIRST TRUE "TRANQUILAXANT"  
**Trancopal®**



case profile no. 3347\* A 35-year-old housewife had a history of severe dysmenorrhea and premenstrual tension: Menarche, age 14; gravida II, Para I; menstrual cycle, fairly regular; pelvic examination, essentially negative results. The patient suffered from severe tension and irritability for from two to seven days before and during menstruation. Cramps were experienced during all three days of the menstrual periods. The analgesics provided limited symptomatic relief.

Trancopal, 200 mg. t.i.d., was prescribed for the dysmenorrhea. Result: Relief of severe cramping and accompanying irritability. Because of these excellent results Trancopal was prescribed for premenstrual tension. Result: Excellent response. This patient has remained on the above regimen for more than six months and no adverse effects have been noted.

**Indications—Musculoskeletal:** Low back pain (lumbago, sacroiliac pain, etc.); neck pain (torticollis); bursitis; rheumatoid arthritis; osteoarthritis; disc syndrome; fibrositis; ankle sprain; tennis elbow; myositis; postoperative muscle spasm. **Psychogenic:** Anxiety and tension states; dysmenorrhea; premenstrual tension; asthma; angina pectoris; alcoholism.

**Dosage:** 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours.

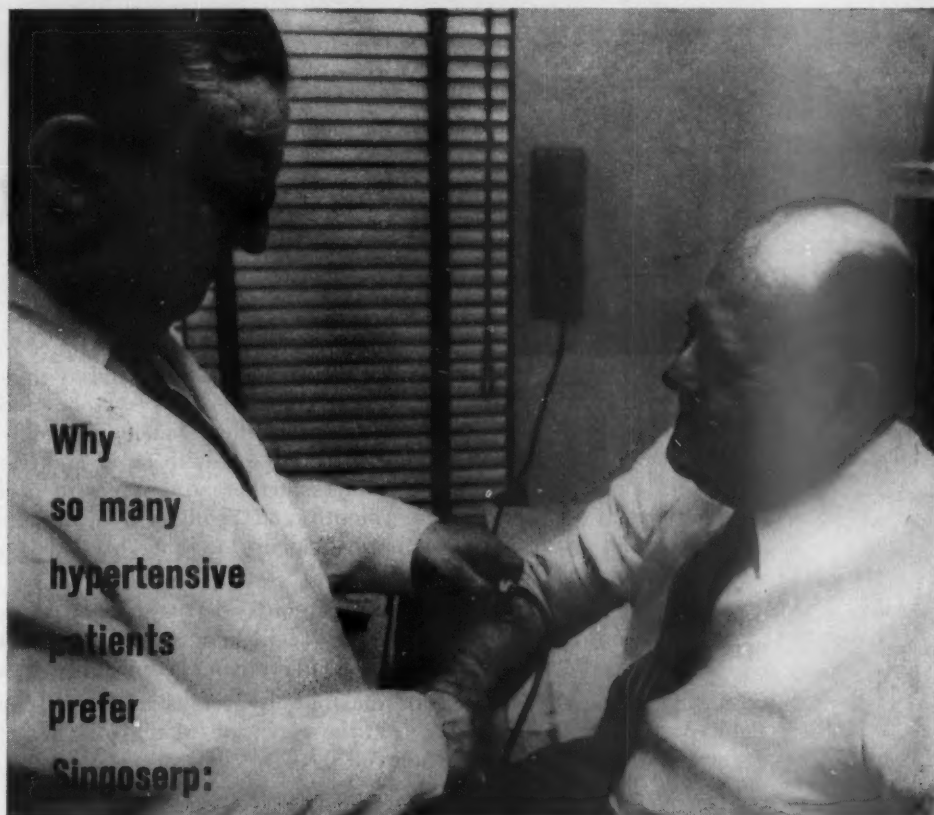
**How Supplied:** Now available in two strengths. Trancopal Caplets®, 100 mg. (peach colored, scored), bottles of 100. New Strength—Trancopal Caplets, 200 mg. (green colored, scored), bottles of 100.

Winthrop  
LABORATORIES  
NEW YORK 18, N.Y.

\*Clinical Report on file at the Department of Medical Research, Winthrop Laboratories.

Trancopal (brand of chlorazepate) and Caplets, trademarks reg. U.S. Pat. Off.

1406M



**Why  
so many  
hypertensive  
patients  
prefer  
Singoserp:**

## **It spares them from the usual rauwolfia side effects**

**FOR EXAMPLE:** "A clinical study made of syrosingopine [Singoserp] therapy in 77 ambulant patients with essential hypertension demonstrated this agent to be effective in reducing hypertension, although the daily dosage required is higher than that of reserpine. Severe side-effects are infrequent, and this attribute of syrosingopine is its chief advantage over other Rauwolfia preparations. The drug appears useful in the management of patients with essential hypertension."\*

\*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.



# **Singoserp®**

(syrosingopine CIBA)

**First drug to try in new hypertensive patients**

**First drug to add in hypertensive patients already on medication**

**SUPPLIED:** Singoserp Tablets, 1 mg. (white, scored); bottles of 100. Samples available on request. Write to CIBA, Box 277, Summit, N. J.



# announcing

*the keystone in a new and*

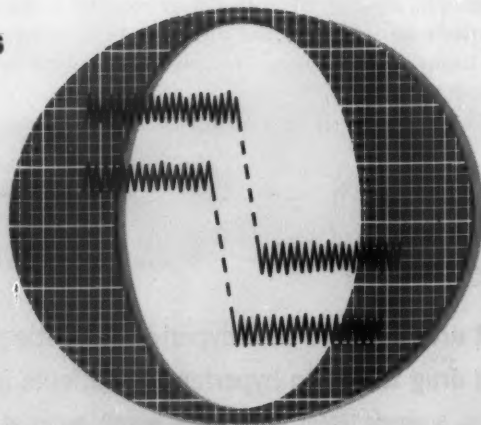
**O**STENSIN is a new oral ganglionic-blocking agent of significance to every physician who treats hypertensive patients. The sympathetic blockade produced with OSTENSIN lowers systolic and diastolic blood pressure with predictable effectiveness and yet—because of minimal parasympathetic action—with fewer and less severe by-effects.<sup>1,2,3</sup> OSTENSIN offers further advantages in oral administration, low dosage, smooth and prolonged antihypertensive action, prompt onset, no evidence of inherent toxicity, and rare drug tolerance.<sup>3</sup>

OSTENSIN, used with chlorothiazide or its derivatives, provides a superior new antihypertensive regimen<sup>1,2,3,4</sup> with reduced dosage, by-effects further decreased, and maximal clinical benefits.

OSTENSIN is indicated in diastolic hypertension. (Diastolic hypertension is defined as "... the elevation of diastolic blood pressure to 90 mm. Hg or above."<sup>5</sup>)

COMPREHENSIVE LITERATURE SUPPLIED ON REQUEST

## TABLETS



Philadelphia 1, Pa.

OSTENSIN is the registered trademark for Trimethidinium Methosulfate, Wyeth.

Please Mention this Journal when writing to Advertisers

## *effective antihypertensive regimen*

### BY-EFFECTS OF THREE OTHER GANGLIONIC-BLOCKING AGENTS<sup>6,7,8</sup> COMPARED WITH THOSE OF OSTENSIN<sup>1,9</sup>

	Other Agents	OSTENSIN
Constipation	59-69% of patients	5% of patients
Postural hypotension	33-59% of patients	37% of patients
Visual disturbances	42-50% of patients	34% of patients
Dry mouth	38-41% of patients	15% of patients

"Of particular interest has been the virtual absence of constipation despite adequate blood pressure control. This finding suggests a lower risk of paralytic ileus. . . ."<sup>1</sup>

Supplied: Tablets, scored, 20 and 40 mg., vials of 100.

1. Dunsmore, R.A., et al.: Am. J. M. Sc. 236:483 (Oct.) 1958. 2. Blaquier, P., et al.: Univ. Michigan M. Bull. 24:409 (Oct.) 1958. 3. Smirk, F.H.: Submitted for publication. 4. Janney, J.F.: Submitted for publication. 5. Council on Drugs, A.M.A.: J.A.M.A. 166:640 (Feb. 8) 1958. 6. Freis, E.D., and Wilson, I.M.: Circulation 13:856 (June) 1956. 7. Moyer, J.H., et al.: A.M.A. Arch. Int. Med. 98:187 (Aug.) 1956. 8. Moyer, J.H., et al.: Am. Pract. & Dig. Treat. 7:1765 (Nov.) 1956. 9. Dunsmore, R.A. In Tislow, R.F., et al.: Scientific Exhibit. Presented at Annual Convention of A.M.A., San Francisco, June 23-27, 1958.

# ostensin<sup>®</sup>

*Ganglionic blockade with fewer and milder by-effects*

Please Mention this Journal when writing to Advertisers



smaller, lighter—  
with greater  
versatility  
than ever!

**EK-III  
dual-speed  
ELECTROCARDIOGRAPH**

The new Burdick dual-speed EK-III is not *miniaturized*! Smaller and lighter, it still produces a sharp, full, standard-sized 5 cm. record — at either 25 mm. or 50 mm. per second!

The unit weighs just 22½ pounds (26½ pounds with all accessories). Compact design and unique carrying handle make the EK-III the ideal instrument for accurate office cardiography, as well as for bedside use.

Investigate the advantages of the new Burdick EK-III. Your Burdick representative will gladly demonstrate the instrument at your convenience... or write directly to the company for complete descriptive material. No obligation, of course.

Routine electrocardiograms are important under age 40 for future comparison; over age 40 for screening.

JAMA, Mar. 28, 1953

**THE BURDICK CORPORATION**

MILTON, WISCONSIN

Branch Offices: NEW YORK • CHICAGO • ATLANTA • LOS ANGELES  
Dealers in all principal cities

New reinforced therapy  
from Schering  
for seasonal asthma  
and allergic dermatoses

## What's its name?

# Polanil

## What's its value?

POLANIL is the combination of the "new" antihistamine, dextro-chlorpheniramine maleate, and the "old" corticosteroid, dexamethasone, in a potent, single-tablet preparation. It's the only tablet of its kind, and it's not hard to see why.

## What tells us so?

POLANIL is the only combination of dextro-chlorpheniramine maleate and dexamethasone available in a single-tablet preparation.

POLARAMINE, the closest to a perfect antihistamine

DERONIL, today's lowest dosage corticosteroid

POLANIL

## What is it?

POLANIL is dextro-chlorpheniramine maleate (Polaramine® Maleate) — the closest to a perfect antihistamine and dexamethasone (Deronil®) — today's lowest dosage corticosteroid.

## What are its advantages?

POLANIL is the only combination of dextro-chlorpheniramine maleate and dexamethasone available in a single-tablet preparation. It's the only tablet of its kind, and it's not hard to see why. POLANIL is the only combination of dextro-chlorpheniramine maleate and dexamethasone available in a single-tablet preparation. It's the only tablet of its kind, and it's not hard to see why.

## How is it scheduled?

POLANIL is the only combination of dextro-chlorpheniramine maleate and dexamethasone available in a single-tablet preparation. It's the only tablet of its kind, and it's not hard to see why.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

Schering

# NEW EVIDENCE SUGGESTS ANOTHER REASON FOR PRESCRIBING TAO

## UNIQUE "STARBURST" EFFECT: TAO METABOLIZES

The impression that TAO is an unusually active antibiotic has steadily gained recognition by impressive clinical performance. Now come reports of *in vivo* and *in vitro* biological and biochemical evaluations that show TAO to be indeed unique.<sup>1,2</sup>

TAO differs from other antibiotics in that it is metabolized to multiple active compounds which remain active throughout their presence in the body. There are 7 of these derivatives . . . and all 7 (in addition to TAO) show activity against common Gram-positive pathogens, including resistant strains of *Staph. aureus*.

In light of these findings, take another look at TAO performance:

- 92% success in published cases of Gram-positive respiratory, skin, soft tissue and genitourinary infection • Effective against 78% of 64 "antibiotic-resistant" epidemic staphylococci. (In the same study, chloramphenicol was active against 52%; erythromycin against only 25%)<sup>3</sup> • No side effects in 94%; infrequent reactions mild and easily reversed • Quickly absorbed • Highly palatable.

**Sound reasons to: Start with TAO to end 9 out of 10 common Gram-positive infections.**

**Supplied:** TAO Capsules — 250 mg., and 125 mg., bottles of 60. TAO for Oral Suspension — 125 mg. per tsp. (5 cc.) when reconstituted; unusually palatable cherry flavor; 60 cc. bottle. Prescription only.

**Other TAO forms available:** TAO Pediatric Drops: flavorful, easy to administer. TAO-AC: TAO analgesic, antihistaminic compound. TAO-MID: TAO with triple sulfas. Intramuscular or Intravenous: in clinical emergencies. Prescription only.

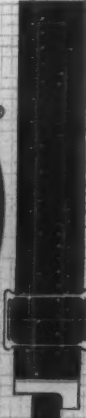
1. English, A. R., and McBride, T. J.: Proc. Soc. Exper. Biol. & Med. 100:880 (Apr.) 1959. 2. Celmer, W. D.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 277. 3. English, A. R., and Fink, F. C.: Antibiotics & Chemother. 8:420 (Aug.) 1958.


designed  
for  
superior  
control  
of  
common  
Gram-  
positive  
infections

# TAO<sup>®</sup>

(TRIACETYLOLEANDOMYCIN)

Capsules/Oral Suspension



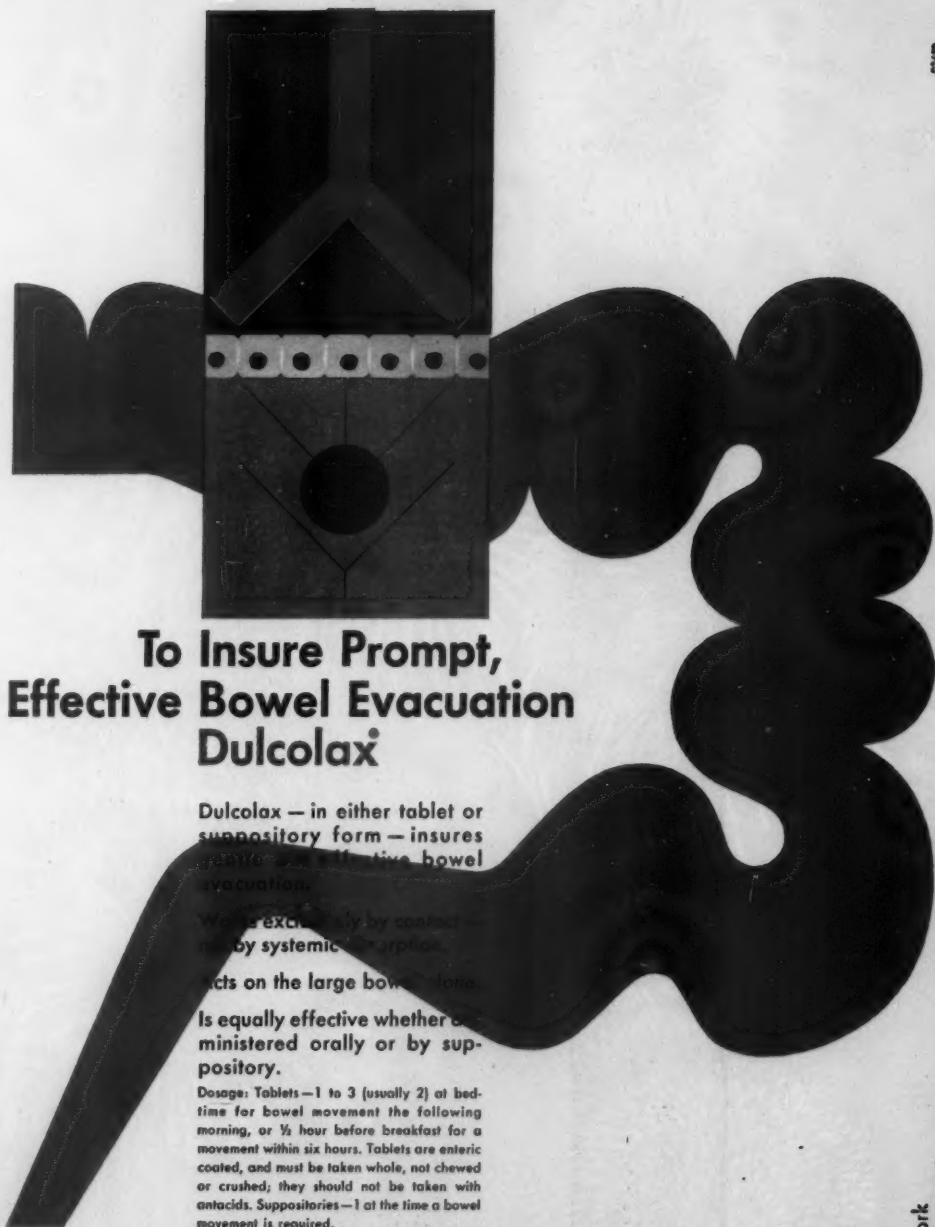


**New York 17, N. Y.**  
 Division, Chas. Pfizer & Co., Inc.  
 Science for the World's Well-Being



## PART 7 BIOLOGICAL ACTIVE DERIVATIVES





## To Insure Prompt, Effective Bowel Evacuation Dulcolax

Dulcolax — in either tablet or suppository form — insures prompt and effective bowel evacuation.

Works exclusively by contact — not by systemic absorption.

Acts on the large bowel alone.

Is equally effective whether administered orally or by suppository.

**Dosage:** Tablets — 1 to 3 (usually 2) at bedtime for bowel movement the following morning, or ½ hour before breakfast for a movement within six hours. Tablets are enteric coated, and must be taken whole, not chewed or crushed; they should not be taken with antacids. Suppositories — 1 at the time a bowel movement is required.

**Supplied:** Dulcolax® (brand of bisacodyl). Yellow enteric-coated tablets of 5 mg. in boxes of 6 and bottles of 100. Suppositories of 10 mg. in boxes of 6. Under license from C. H. Boehringer Sohn, Ingelheim.

### Contact Laxative

### Geigy

Ardley, New York

start  
low...

**DBI**

the "follow-up" oral hypoglycemic agent  
... safely lowers blood sugar in mild, moderate  
and severe diabetes, in children and adults

# .go slow

The "Start Low! Go Slow!" dosage pattern with DBI enables a maximum number of diabetics to enjoy the convenience, comfort and satisfactory regulation of oral therapy in:

- stable adult diabetes
- unstable (brittle) diabetes
- juvenile diabetes
- sulfonylurea resistant diabetes

"Start Low! Go Slow" means low initial dosage (25 mg., or 50 mg. in divided doses, per day) with small dosage increments (25 mg.) every 3rd or 4th day until blood sugar levels are adequately controlled. Injected insulin is reduced gradually with each increase in DBI dosage. Satisfactory regulation of mild stable diabetes is usually achieved with DBI alone.\*

On "Start Low! Go Slow!" dosage, DBI is relatively well tolerated.

Over 2000 diabetics have been carefully studied on DBI daily for varying periods up to three years. No physiologic or functional changes in liver, blood, kidneys, heart or other organs were seen.

DBI (DL-phenethylbiguanide) is available as white, scored tablets of 25 mg. each, bottles of 100.

\*Send for brochure with complete dosage instructions for each class of diabetes, and other pertinent information.

## DBI

Trademark,  
brand of  
Pharmaline HCl

U. S. Vitamin & Pharmaceutical Corp.  
Arlington Park Laboratories, Division  
280 East 47th St., New York 17, N. Y.

## *New* agent for parkinsonism



# Akineton®

brand of biperiden



### PARKINSON'S DISEASE

postencephalitic — idiopathic — arteriosclerotic

### DRUG-INDUCED EXTRAPYRAMIDAL DISORDERS

parkinsonism — dyskinesia — akathisia

### MUSCULAR SPASTICITY NOT RELATED TO PARKINSONISM

#### ACTION

Frequently diminishes akinesia, rigidity, and tremor with subsequent improvement in coordinated movement, gait, and posture. Masklike face disappears. Salivation and oily skin are decreased. Oculogyric crises are often lessened in intensity and frequency.

#### SIDE EFFECTS

Minimum (mainly dry mouth or blurred vision).

#### DOSAGE

Individual adjustment of dosage is necessary in all instances. Dose range extends from 2 mg. to 24 mg. daily, in divided doses.

#### AVAILABLE

Supplied as the hydrochloride salt, 2 mg. bisected tablets, bottles of 100 and 1000.

Complete information furnished upon request.

**KNOLL PHARMACEUTICAL COMPANY**

(formerly Bilhuber-Knoll Corp.)

**ORANGE  
NEW JERSEY**



# RAUDIXIN

Raudixin—the cornerstone of antihypertensive therapy—  
helps relieve the pressures in your patients—helps  
relieve the pressures on your patients / 50 and 100 mg. tablets  
whole root rauwolfia for exceptional patient response

**SQUIBB**



Squibb Quality—the Priceless Ingredient

Squibb Whole Root Rauwolfia Serpentina/RAUDIXIN® is a SQUIBB TRADEMARK

safely control the "target symptoms" of  
emotional stress with the smallest effective dosage  
(0.25 mg. b.i.d.) of any neuroleptic\* agent



*the promise of*

PERMITIL<sup>®</sup>

Fluphenazine dimethacrylate

*in everyday office practice*



## Primer on PERMITIL

### Q Why another psychopharmacologic agent?

A. The ever-expanding role of chemistry in the treatment of mental and emotional problems in this new era of psychopharmacologic drugs is amply attested to by the growing number of rauwolfia, mephenesin, diphenylmethane and phenothiazine derivatives now in clinical use. When one considers the wide range of indications to be treated—from severe psychosis to mild situational stress—it becomes somewhat clearer as to the reason for the number and diversity of drugs available. In addition, improvements and refinements of existing agents are constantly taking place. Drugs tailored to perform a selected, single function are emerging. So it is with PERMITIL.

### Q Why another phenothiazine?

A. All members of this group contain a phenothiazine nucleus and a side chain attached to the nitrogen atom. Differences in potency are related to specific chemical alterations in these compounds. Clinical evidence demonstrates that the phenothiazines act principally, but to varying degrees, on several subcortical areas of the brain. Thus, certain of these drugs produce sedation and potentiate the action of barbiturates, while others do not; autonomic side effects (such as blurred vision, constipation) are produced by some and not by others; some have been shown to be very effective antiemetic agents. At certain dosage levels, the phenothiazine derivatives also may cause extrapyramidal side effects. These, however, are neuropharmacologic rather than toxic effects and are totally reversible.

Since there is a correlation between the dosage of a phenothiazine derivative and the frequency and the type of side effects it causes, *the less of the drug needed to achieve therapeutic results, the less likely are serious side effects.* Thus, the lower the effective dosage of a phenothiazine derivative, the lower the incidence of unwanted side reactions and, conversely, the higher the level of therapeutic response.

For these reasons, the search has been unceasing to develop a phenothiazine with an optimum therapeutic ratio.

### Q What is a "neuroleptic" agent?

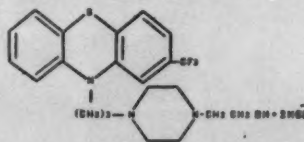
A. The term "neuroleptic" implies a specific effect of a pharmacologic agent on the nervous system. It refers to a mode of action on specific subcortical areas which strongly influence emotional behavior in contradistinction to hypnotic agents which dull the senses. Neuroleptics achieve control of anxiety symptoms without inducing either somnolence or euphoria. Thus, there is an increase in the patient's capacity to cope with life's problems more successfully. The terms "tranquilizers" and "ataraxics" are descriptively impressive, but they fail to convey what seems pharmacologically unique.

### Q Why introduce the term "neuroleptic"?

A. Because it has a precise psychopharmacologic meaning and is more descriptive of the action of PERMITIL than any other current term.

### Q What is PERMITIL?

A. PERMITIL is a new anti-anxiety agent of extraordinary potency and effectiveness. Chemically, PERMITIL is 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine dihydrochloride. The structural formula is:

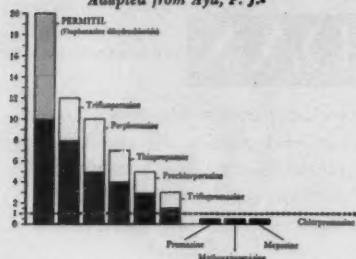


### Q Why is PERMITIL unique?

A. Although PERMITIL can be broadly classified as a phenothiazine, it exhibits a spectrum of unique effects at unprecedented low dosage—a feature that markedly distinguishes this compound from other anti-anxiety drugs.

### The Relative Therapeutic Potency of Various Phenothiazines

Adapted from Ayd, F. J.<sup>2</sup>



The potency of each drug was determined by the criteria proposed by Freyhan.<sup>2</sup> These were: (1) the attainable level of psychomotor inhibition, (2) the speed of action, and (3) the dosage required to obtain effective action.

### Q What are the distinctive clinical advantages of PERMITIL?

A. Extensive clinical studies have established important psychopharmacologic advantages for PERMITIL.

1. The effective dosage of PERMITIL (0.25 mg. b.i.d.) is the lowest safe dosage of any anti-anxiety agent. Since fractional milligram doses of PERMITIL usually produce a therapeutic effect, many of the annoying side effects of the other phenothiazines, which are dose-related, occur less frequently or not at all. In fact, any side effects associated with dosage not exceeding 1 mg. per day have been uncommon and transitory. PERMITIL represents an advance over its predecessors<sup>1</sup> because of its higher level of therapeutic response and low order of side reactions.

2. Unlike other phenothiazines, PERMITIL alleviates symptoms of anxiety, tension, agitation and emotional unrest *without* depressant effect, impaired alertness or slowed intellectual function. Furthermore, anxiety-induced symptoms of apathy, indifference, listlessness, reduced initiative and chronic emotional fatigue (often refractory to other phenothiazines) frequently respond to administration of PERMITIL. Thus, a significantly wider spectrum of "target symptoms" amenable to therapy is an outstanding property of PERMITIL.

3. Onset of action is rapid and patients soon become more relaxed and less tense. The patient regains a more confident outlook and normal drive is restored.

4. PERMITIL has an inherently long duration of effect. This makes possible a particularly convenient and easy-to-remember schedule of morning and evening dosage.

### Q For what, specifically, is PERMITIL indicated?

A. PERMITIL is indicated for the control of the "target symptoms" of emotional stress so common in everyday office practice. The basic areas of usefulness for PERMITIL are: (1) behavioral disturbances characterized by anxiety, tension, apprehension and instability, as well as depressive symptoms associated with anxiety states; (2) emotional stress accompanying organic disorders and complicating recovery from, or acceptance of, the underlying condition; (3) chronic disorders in which anxiety and stress are contributing factors, e.g., gastrointestinal dysfunctions, neurodermatitis, asthma, premenstrual tension, arthritis, hypertension and tension headache.

### Q Is the dosage schedule, as with many phenothiazine derivatives, complex and complicated?

A. No. PERMITIL has an inherently long duration of effect so that twice-a-day dosage provides the patient with day and night symptom alleviation. The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day. This may be increased to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms who have had a trial of lower dosages first that were well tolerated but were only partially effective. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. (Dosage for children has not been established.)

### Q What about side effects and contraindications to PERMITIL?

A. At the recommended dosage of PERMITIL, side effects have been observed infrequently or not at all. PERMITIL, as with other phenothiazines, is contraindicated in severely depressed states.

### Q How is PERMITIL supplied?

A. PERMITIL is available as Tablets, 0.25 mg., bottles of 50 and 500.

References: 1. Ayd, F. J.: The current status of major tranquilizers, in press. 2. Freyhan, F. A.: Therapeutic implications of differential effects of new phenothiazine compounds, *Am. J. Psychiat.* 115:577-585 (Jan.), 1959.

WHITE LABORATORIES, INC.,  
KENILWORTH, NEW JERSEY



*for laxative results without laxative harshness*

**in surgery, hospitalized  
or inactive patients**

**DOXHDAN**

THE SURFACTANT LAXATIVE

Restores normal bowel function by producing soft, easily passed stools gently assisted to defecation with the least possible disturbance to normal body physiology. Evacuation is without strain or trauma — no “griping” or cramping — no bowel distention, no oily leakage or interference with essential food elements. Patient care is made much easier.

**DOSAGE:** For adults and children over 12, one or two capsules. For children, age 6 to 12, one capsule. Administered at bedtime for 2 or 3 days or until bowel movements are normal. Supplied in bottles of 30 and 100 soft gelatin capsules.



**LLOYD BROTHERS, INC.**

CINCINNATI 3, OHIO



## FROM NEW **YOU CAN EXPECT MORE** **POLARAMINE® EXPECTORANT**

Because POLARAMINE Expectorant — Polaramine plus *d*-isoeophedrine sulfate and glyceryl guaiacolate — Restores congested mucous membranes of the entire respiratory tract to normal...gently, rapidly...within only 15 to 30 minutes

■ Relieves unproductive coughing by increasing respiratory tract fluid output and by facilitating expectoration ■ Treats effectively the allergic components of respiratory illness ■ Is *delicious*...a new, different flavor.

POLARAMINE Expectorant is particularly valuable for the relief of coughs and complications of allergic conditions and the allergic manifestations of respiratory illnesses.

Each teaspoonful (5 cc.) of POLARAMINE Expectorant contains 2 mg. POLARAMINE Maleate (dextrochlorpheniramine maleate), 20 mg. *d*-isoeophedrine sulfate and 100 mg. glyceryl guaiacolate.

**Dosage:** Adults, 1 or 2 teaspoonfuls, 3-4 times daily; Children, ½ or 1 teaspoonful, 3-4 times daily.

**Supply:** 16 oz. bottles. SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

*Schering*  
EN-1490-9



# KOLANTYL

**Provides 4 necessary healing actions in one medication<sup>1</sup>...** 1. stops spasm — relieves pain; 2. neutralizes acid — with prompt-acting, long-lasting anti-acid combination free of constipation or laxation; 3. halts erosion — curbs necrotic effects of pepsin and lysozyme; 4. promotes healing — with soothing, protective coating on ulcerated area.

Dosage: 1 tablespoonful gel, or 2 tablets, every three hours as needed.

1. Hufford, A. R.: Rev. of Gastroenterology 18:588.

Formula: each tablet or 10 cc. gel contains —  
 Bentyl (dicyclomine) hydrochloride . . . 5 mg.  
 Aluminum hydroxide gel . . . . . 400 mg.  
 Magnesium oxide . . . . . 200 mg.  
 Methylcellulose . . . . . 100 mg.  
 Sodium lauryl sulfate . . . . . 25 mg.

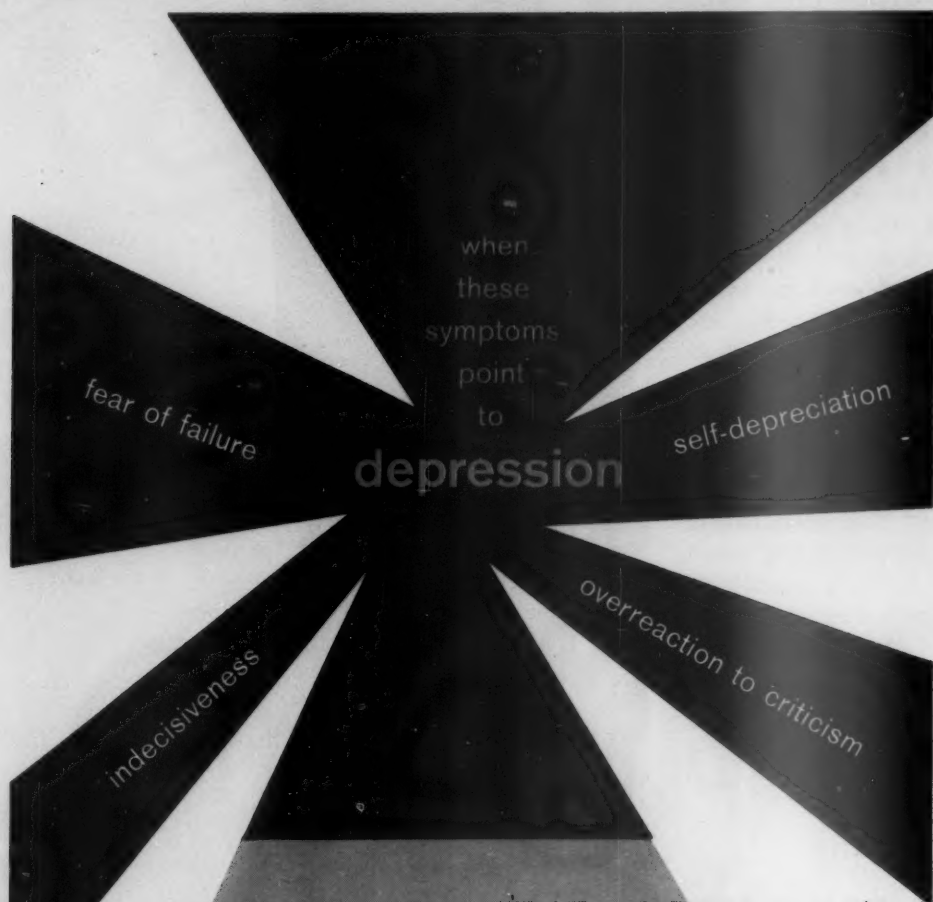
**THE WM. S. MERRELL COMPANY**  
 New York • Cincinnati • St. Thomas, Ontario

TRADEMARK: KOLANTYL®

pleasant-  
tasting,  
mint-  
flavored

**KOLANTYL GEL**





**Dexamyl\***—through its mood-improving and antidepressant action—helps smooth your patient's adjustment to daily living. And, because 'Dexamyl' induces a sense of well-being, it often helps the depressed patient become more responsive to your counselling.

'Dexamyl', a combination of 'Dexedrine' (dextro-amphetamine sulfate, S.K.F.) and amobarbital, is available as tablets, elixir and Spansule\* sustained release capsules.

\* \* \*

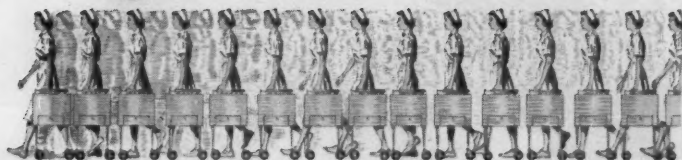
When listlessness and lethargy accompany depression, the gentle stimulation of **Dexedrine\*** helps revive normal interest, activity and capacity for work.

'Dexedrine' is available as tablets, elixir and 'Spansule' sustained release capsules.



SMITH KLINE & FRENCH LABORATORIES

\*T.M. Reg. U.S. Pat. Off.



## A COMPLETE HEART STATION ON WHEELS

with 2 recording speeds • 3 sensitivities • provision for recording other waveforms • provision for visual monitoring

Almost without effort, this modern functional electrocardiograph can be wheeled noiselessly from room to room . . . around beds . . . into and out of elevators. Here are all the diagnostic advantages of the new Model 100 Viso-Cardiette electrocardiograph in a mobile console cabinet of hand-rubbed mahogany or rugged stain-proof light beige plastic laminate. Elec-

trodes, Redux paste and all accessories — and the built-in automatic-retracting power cord — stay with the 100M Mobile Viso. For hospital, clinic or office use, this newest Sanborn electrocardiograph offers the ultimate in diagnostic usefulness and operating convenience. Model 100M Mobile Viso, \$895 delivered, continental U.S.A.

... the recently announced Model 100 Viso in a handsome mahogany case, price \$850 delivered, continental U.S.A. You can convert your present table-top 100 Viso into the mobile unit of your choice at any time by purchasing the new 100M mobile cabinet separately. (Price, \$120 delivered, continental U.S.A.)



Model 300 Visette — only 18 pounds complete, briefcase size. You or your nurse can carry this truly portable instrument anywhere . . . ideal for "on-call" ECG work. Price \$625 delivered, continental U.S.A.

Complete descriptive literature on request.

## SANBORN COMPANY

MEDICAL DIVISION • 175 Wyman St., Waltham 54, Massachusetts

Please Mention this Journal when writing to Advertisers

## common denominator: a.p.

Worlds apart—plumber, pediatrician, press agent, counterman—these people have one thing in common: angina pectoris. Each one is receiving Peritrate 20 mg. q.i.d. as "basic therapy," providing long-acting coronary vasodilatation for fewer, less severe attacks, increased exercise tolerance, and reduced nitroglycerin dependence.

In one or another, however, underlying apprehensions, sudden stress situations, unpredictable daily schedules call for "basic therapy" plus individualized treatment. Broad coverage protection for each patient is afforded by a Peritrate formulation in terms of

adaptable  
aprophylaxis  
in  
apngina  
apectoris

# Peritrate®

brand of pentaerythritol tetranitrate



MORRIS PLAINS, N.J.

"basic therapy"  
Peritrate 20 mg.

for the apprehensive patient  
Peritrate with Phenobarbital

for congestive failure  
Peritrate with Aminophylline

for convenient 24-hour protection  
Peritrate Sustained Action

to relieve the acute attack  
Peritrate with Nitroglycerin

Please Mention this Journal when writing to Advertisers

# IS THIS YOUR PATIENT?

1.



## EARLY POSTMENOPAUSE

Complains of low back pain, vague aches and fatigue  
Posture is poor  
No x-ray evidence of bone lesions

2.



## LATER POSTMENOPAUSE

Back pain is severe, spreading to hips ("girdle pain")  
Patient is round shouldered, walks with a stoop  
X-ray reveals compression fractures of lower vertebrae

3.



## 70 AND OVER

Fracture of hip after a minor fall  
X-ray reveals fracture of neck of femur  
X-ray reveals compression fractures of lower lumbar vertebrae

These three patients have osteoporosis. Early diagnosis and treatment with "Formatrix" is important because osteoporosis is probably the only age change that can be averted. With "Formatrix" therapy, relief from the symptoms of *low back pain, vague aches* and *fatigue* may be obtained in as little as a few weeks. "Formatrix" supplies the essential materials to stimulate increased bone formation and prevent further loss of bone substance that leads eventually to loss of height, stooped posture, and disabling fractures.

The highest incidence of osteoporosis may be found among the 14,000,000 women in the U.S.A. who are 55 years of age and over. Some investigators claim that almost all women past the menopause will show some degree of osteoporosis; furthermore, if all these women were examined carefully, 50 per cent would show x-ray evidence of decreased bone mass.

Suspicion may be the handiest diagnostic tool since presenting symptoms vary from mild to severe and incapacitating pain, and no x-ray evidence of spinal degeneration is available until about 30 per cent of the bone matrix is lost. Between these two extremes there are other signs of estrogen deficiency such as *wrinkled and thinning skin*, a *tendency to appear older than stated years*; there may also be *hypercalciuria* when postmenopausal osteoporosis is complicated by acute osteoporosis of disuse.

Osteoporosis is primarily an atrophic condition of bone matrix formation and any factor that depresses osteoblastic activity or retards the formation of protein and connective tissue such as *prolonged immobilization, cortisone therapy, or malnutrition* will favor development of osteoporosis in both male and female.



AYERST LABORATORIES  
New York 16, N. Y. • Montreal, Canada

# NEW

"FORMATRIX" contains three most essential bone building materials necessary for matrix formation, estrogen, androgen and vitamin C.

The estrogen component of "Formatrix" stimulates osteoblastic activity, thus aiding calcium and phosphorus deposition; it also imparts a feeling of "well-being." The anabolic action of methyltestosterone promotes the synthesis of protein and restores a positive

nitrogen balance. Together, these hormones have a greater effect on bone and protein metabolism than either alone, and side effects are minimized because of the opposing action of the two steroids on sex-linked tissues. Vitamin C plays an important role in formation of intercellular cement substance and amino acid synthesis. "Formatrix" has a large amount of vitamin C to aid in new bone matrix formation and to further help in the healing of fractures.

**"FORMATRIX" — each tablet contains:**

Conjugated estrogens equine ("Premarin"®).....	1.25 mg.
Methyltestosterone.....	10.0 mg.
Ascorbic acid.....	400.0 mg.

Dosage: 1 tablet a day — In the female, three weeks of treatment with a rest period of one week between courses is recommended.

Supplied: Tablets, bottles of 60 and 500.

LITERATURE AVAILABLE ON REQUEST

1.



**EARLY POSTMENOPAUSE**  
No x-ray evidence of bone lesion

2.



**LATER POSTMENOPAUSE**  
X-ray reveals compression fracture of lower vertebrae

3.



**70 AND OVER**  
X-ray reveals fracture of neck of femur

TO RELIEVE LOW BACK PAIN — TO PROMOTE HEALING OF FRACTURES

*in osteoporosis*

# 'FORMATRIX'

(Brand of Steroid — Vitamin Combination)

for matrix formation



*"...which antacid? Rorer's Maalox. Excellent results, no constipation plus a pleasant taste that patients like."*

.....

MAALOX® an efficient antacid suspension of magnesium-aluminum hydroxide gel offered in bottles of 12 fluidounces.

TABLET MAALOX: 0.4 Gram (equivalent to one teaspoonful), Bottles of 100.

TABLET MAALOX No. 2: 0.8 Gram, double strength (equivalent to two teaspoonfuls), Bottles of 50 and 250.

Samples on request.

WILLIAM H. RORER, INC., Philadelphia 44, Pennsylvania

Please Mention this Journal when writing to Advertisers



OFFERS HIGHER BLOOD  
LEVELS - FASTER - THAN  
ANY OTHER SALT OF  
ORAL PENICILLIN:  
**COMPOCILLIN®-VK**

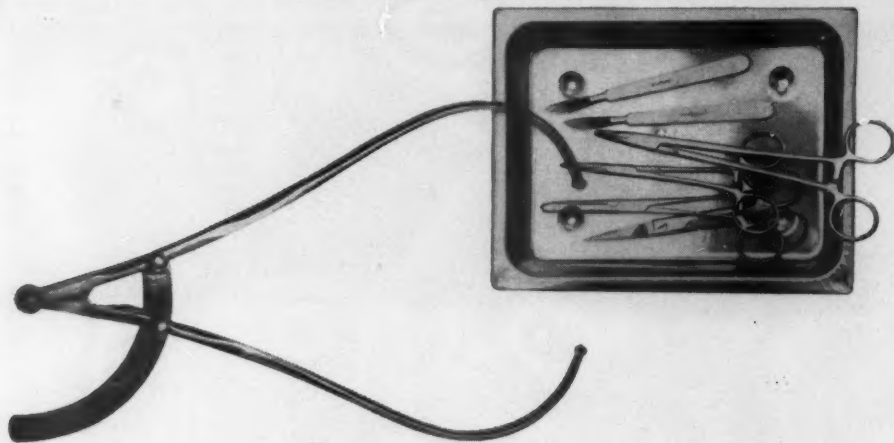
Potassium Penicillin V

© FILMTAB — FILM-SEALED TABLETS, ABBOTT, U.S. PAT. NO. 2,861,065

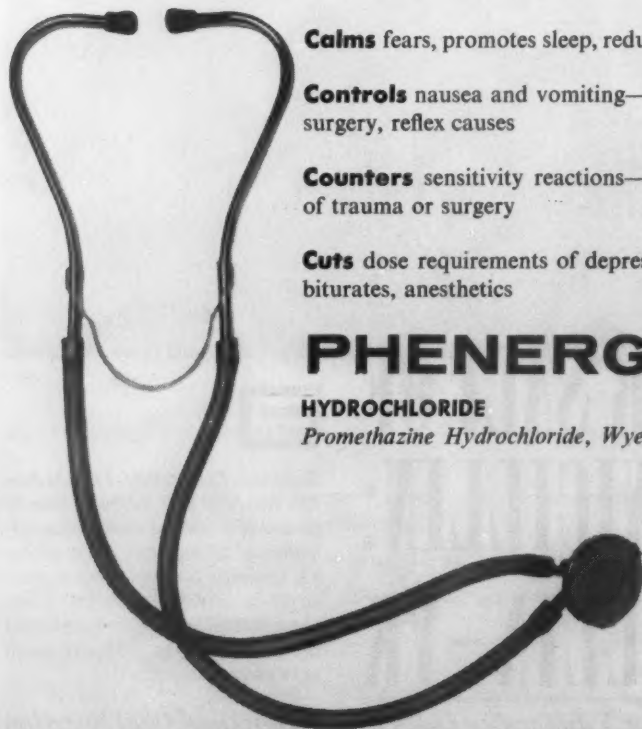


Supplied: Compocillin-VK Filmtabs, 125 mg. (200,000 units), bottles of 50 and 100; 250 mg. (400,000 units), bottles of 25 and 100. Compocillin-VK Granules for Oral Solution come in 40-cc. and 80-cc. bottles. When reconstituted, each 5-cc. teaspoonful represents 125 mg. (200,000 units) of potassium penicillin V.

*in tiny, easy-to-swallow Filmtabs® in tasty, cherry-flavored Oral Solution*



In  
MEDICINE  
SURGERY  
OBSTETRICS



**Calms** fears, promotes sleep, reduces postoperative excitement

**Controls** nausea and vomiting—motion sickness, pregnancy, surgery, reflex causes

**Counters** sensitivity reactions—allergy, drugs, tissue edema of trauma or surgery

**Cuts** dose requirements of depressant agents—narcotics, barbiturates, anesthetics

**PHENERGAN®**

**HYDROCHLORIDE**

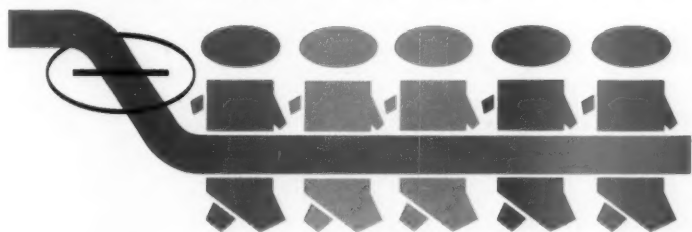
*Promethazine Hydrochloride, Wyeth*

TABLETS  
SYRUP  
SUPPOSITORIES  
INJECTION



Philadelphia 1, Pa.

*the oral antidiabetic most likely to succeed*



# DIABINESE®

brand of chlorpropamide

The superior effectiveness of DIABINESE increases the chance of success of oral therapy in your diabetic patients. Moreover, in properly regulated dosage, DIABINESE is free from significant incidence of serious side effects. Incidentally, your patients will appreciate the economy possible (savings up to 50%) when DIABINESE is the oral therapy selected.

**Pfizer** Science for the world's well-being™

*when other oral therapy has failed...*

"Comparison of diabetic control between tolbutamide and chlorpropamide in the same patients shows that good control often can be achieved with chlorpropamide when tolbutamide has been proved ineffective."

Lee, C. T., Jr.; Schless, G. L., and Duncan, G. G.:  
Ann. New York Acad. Sc. 74:798, 1959.

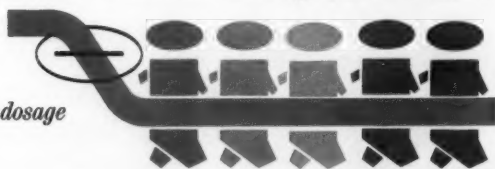
*also successful when replacement or reduction of insulin is desirable . . . and when dietary control proves impractical*

# DIABINESE®

brand of chlorpropamide

*the oral antidiabetic most likely to succeed*

*economical once-a-day dosage*



*available as 100 mg. and 250 mg. tablets*

For complete information write to the Medical Department, PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, N. Y.

and other  
allergies  
take over

# METRETON

"Meti" steroid-antihistaminic

## for rapid relief systemically—METRETON Tablets—

in drug reactions, urticaria, angioedema, atopic and contact dermatitis, allergic eczema, ocular allergies, serum sickness

## topically for allergic rhinitis—METRETON Nasal Spray

## topically for eye allergies—

## METRETON Ophthalmic Suspension

### supplied

**METRETON® Tablets**, bottles of 30 and 100. Each METRETON Tablet contains 2.5 mg. prednisone, 2 mg. chlorprophenpyridamine maleate, and 75 mg. ascorbic acid.

**METRETON Nasal Spray**, 15 cc. squeeze bottle. Each cc. of METRETON Nasal Spray contains 2 mg. (0.2%) prednisolone acetate and 3 mg. (0.3%) chlorprophenpyridamine gluconate.

**METRETON Ophthalmic Suspension**, 5 cc. dropper bottle. Each cc. of METRETON Ophthalmic Suspension contains 2 mg. (0.2%) prednisolone acetate and 3 mg. (0.3%) chlorprophenpyridamine gluconate.

Meti,® brand of corticosteroids.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

*Schering*

# PROVEN EFFECTIVE FOR THE TENSE AND NERVOUS PATIENT



“There is perhaps no other drug introduced in recent years which has had such a broad spectrum of clinical application as has meprobamate.\* As a tranquilizer, without an autonomic component in its action, and with a minimum of side effects, meprobamate has met a clinical need in anxiety states and many organic diseases with a tension component.”

Krantz, J. C., Jr.: The restless patient — A psychologic and pharmacologic viewpoint.  
Current M. Digest  
25:68, Feb. 1958.

## • Miltown®



the original meprobamate, discovered and introduced by  
WALLACE LABORATORIES, New Brunswick, N. J.

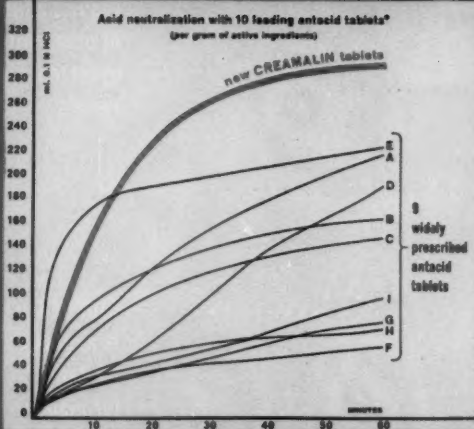
THE MOST SIGNIFICANT IMPROVEMENT IN  
ANTACID THERAPY SINCE THE INTRODUCTION  
OF ALUMINUM HYDROXIDE IN 1929

**NEW**

# Creamalin<sup>®</sup> ANTACID TABLETS

## CREAMALIN NEUTRALIZES MORE ACID FASTER

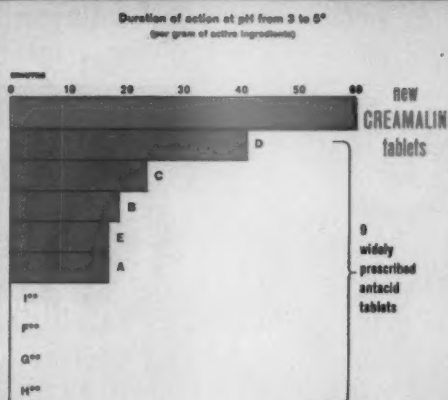
Quicker Relief • Greater Relief



\*Tablets were powdered and suspended in distilled water in a constant temperature container (37°C) equipped with mechanical stirrer and pH electrodes. Hydrochloric acid was added as needed to maintain pH of 3.5. Volume of acid required was recorded at frequent intervals for one hour.

## CREAMALIN NEUTRALIZES MORE ACID LONGER

More Lasting Relief



\*Finkels, E. T., Jr., Fisher, M. P. and Tobias, M. L. A new highly reactive aluminum hydroxide complex for gastric hyperacidity. To be published.

\*Not plotted below 5.

Each Creamalin Antacid Tablet contains 320 mg. specially processed, highly reactive, short polymer dried aluminum hydroxide gel, (stabilized with hexitol), with 75 mg. magnesium hydroxide.

1. Neutralizes acid faster (quicker relief)
2. Neutralizes more acid (greater relief)
3. Neutralizes acid longer (more lasting relief)
4. No constipation • No acid rebound
5. More pleasant to take



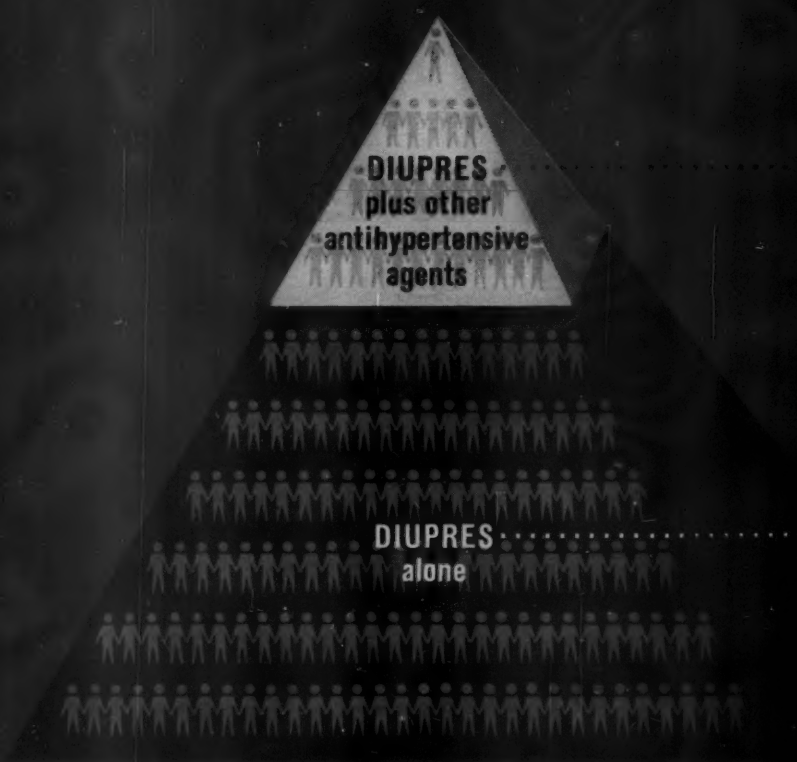
No chalky taste. New CREAMALIN tablets are not chalky, gritty, rough or dry. They are highly palatable, soft, smooth, easy to chew, mint flavored.

**Adult Dosage:** Gastric hyperacidity—2 to 4 tablets as necessary. Peptic ulcer or gastritis—2 to 4 tablets every two to four hours. Tablets may be chewed, swallowed with water or milk, or allowed to dissolve in the mouth.

**Supplied:** Bottles of 50, 100, 200 and 1000.

Winthrop

LABORATORIES • NEW YORK 18, NEW YORK



with DIUPRES,  
fewer patients  
require addition  
of other anti-  
hypertensive  
agents

DIUPRES  
is adequate  
by itself  
for many  
hypertensives

DIUPRES PROVIDES "BROAD-BASE" ANTIHYPERTENSIVE THERAPY

... is effective by itself in a majority of patients with mild or moderate  
hypertension, and even in many with severe hypertension

greatly improved  
and simplified management  
of  
hypertension

# DIUPRES<sup>®</sup>

DIURIL<sup>®</sup> WITH RESERPINE

the first "wide-range" antihypertensive—effective in mild, moderate, and severe hypertension

- more hypertensives can be better controlled with DIUPRES alone than with any other agent... with greater simplicity and convenience, and with decreased side effects
- can be used as total therapy or primary therapy, adding other drugs if necessary
- in patients now treated with other drugs, can be used as replacement or adjunctive therapy
- should other drugs need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced
- organic changes of hypertension may be arrested and reversed... even anginal pain may be eliminated
- patient takes one tablet rather than two... dosage schedule is easy to follow
- economical

## DIUPRES-500

500 mg. DIURIL (chlorothiazide),  
0.125 mg. reserpine.

One tablet one to three times a day.

## DIUPRES-250

250 mg. DIURIL (chlorothiazide),  
0.125 mg. reserpine.

One tablet one to four times a day.



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

DIUPRES and DIURIL (CHLOROTHIAZIDE) ARE TRADEMARKS OF MERCK & CO., INC.



# NEW—DELICIOUS—ORANGE-FLAVORED PENTIDS "400" FOR SYRUP

Squibb Flavored Penicillin Powder

**Tastes Good...** delicious, refreshing orange flavor means ready acceptance by young or "finicky" patients.

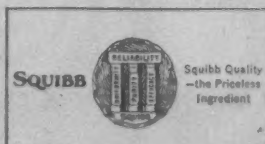
**Double Potency...** 400,000 units of potassium penicillin G per teaspoonful ...no other form of oral penicillin gives better therapeutic results.

**Economical...** more economical for your patients than other forms of penicillin. Where double strength Pentids is required for treatment of severe penicillin-susceptible infections due to hemolytic streptococcus, pneumococcus, staphylococcus, and for prevention of streptococcal infections in patients with a history of rheumatic fever, Pentids "400" will save your patients' money.

**Convenient...** Pentids "400" for Syrup, soluble powder containing penicillin G potassium [buffered], which when reconstituted with 35 cc. of water provides 60 cc. of orange-flavored syrup with a potency of 400,000 units per 5 cc. teaspoonful.

"PENTIDS" IS A SQUIBB TRADEMARK

Also available: *Pentids "400"*: 400,000 units of buffered penicillin G potassium per scored tablet. *Pentids*: 200,000 units of buffered penicillin G potassium per scored tablet. *Pentids for Syrup*: 200,000 units of penicillin G potassium per teaspoonful (5 cc.). *Pentids Capsules*: 200,000 units of penicillin G potassium per capsule. *Pentids Soluble Tablets*: 200,000 units of penicillin G potassium per tablet. *Pentids-Sulfas Tablets*: 200,000 units of penicillin G potassium with 0.5 Gm. triple sulfas per tablet.

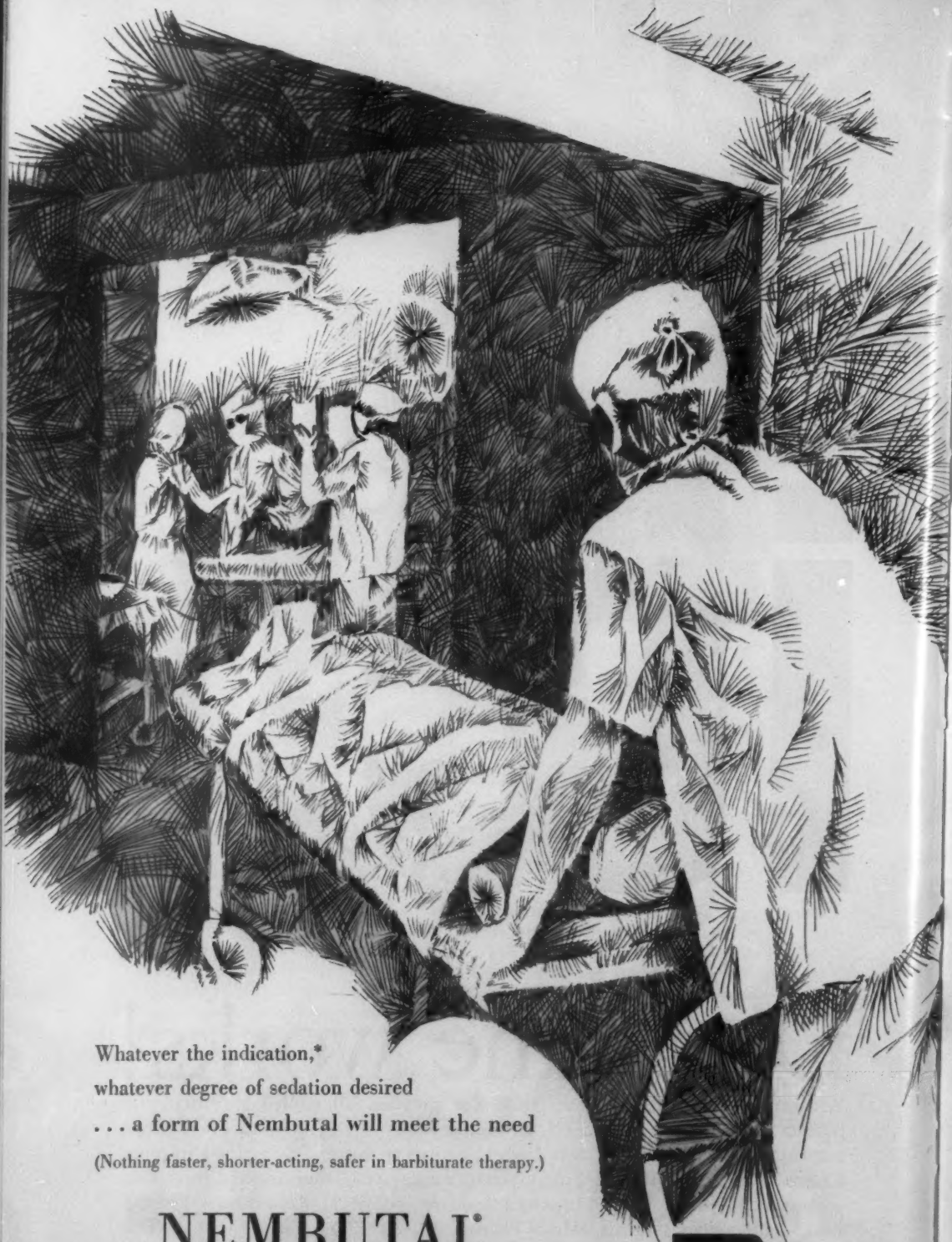


# allergic itch

## Dimetane® works!

Whatever the allergic symptom, Dimetane provides unexcelled antihistaminic potency and minimal side effects. Dimetane works in certain cases where other antihistamines fail. For your next case of pruritus or urticaria prescribe Dimetane Extentabs® (12 mg.), Tablets (4 mg.), Elixir (2 mg./5 cc.), Dimetane-Ten Injectable (10 mg./cc.) or Dimetane-100 Injectable (100 mg./cc.). A. H. Robins Co., Inc., Richmond 20, Virginia/Ethical Pharmaceuticals of Merit Since 1878





Whatever the indication,\*  
whatever degree of sedation desired  
... a form of Nembutal will meet the need  
(Nothing faster, shorter-acting, safer in barbiturate therapy.)

## NEMBUTAL

(Pentobarbital, Abbott)

\*PREOPERATIVE SEDATION



## In Coronary Insufficiency...

Your high-strung angina patient often expends a "100-yd. dash" worth of cardiac reserve through needless excitement.



Curbs emotion  
as it boosts  
coronary  
blood supply

CONTROL OF EMOTIONAL  
EXERTION with Miltrate  
leaves him more freedom  
for physical activity.

IMPROVED CORONARY BLOOD  
SUPPLY with Miltrate  
increases his exercise tolerance.

# Miltrate\*

Miltown® (meprobamate) + PETN

Each tablet contains: 200 mg. Miltown and  
10 mg. pentaerythritol tetranitrate.

Supplied: Bottles of 50 tablets.

Usual dosage: 1 or 2 tablets q.i.d. before meals  
and at bedtime. Dosage should be individualized.



WALLACE LABORATORIES • New Brunswick, N. J.



# TO STOP DIARRRHEA

from all points... growing evidence favors

# FUROXONE®

brand of furazolidone

■ Pleasant-flavored LIQUID, 50 mg. per 15 cc. (with kaolin and pectin) ■ Convenient TABLETS, 100 mg. ■ Dosage—400 mg. daily for adults, 5 mg./Kg. daily for children (in 4 divided doses).



**From a Large Midwestern University: FUROXONE Controls Antibiotic-Resistant Outbreak.** An outbreak of bacillary dysentery due to *Shigella sonnei* was successfully controlled with FUROXONE after a broad-spectrum antibiotic had proved inadequate. Cure rates (verified by stool culture) were 87% with FUROXONE, 36% with chloramphenicol. Only FUROXONE "failures" were those lost to follow-up. Chloramphenicol failures subsequently treated with FUROXONE responded without exception. FUROXONE was also used effectively as prophylaxis and to eliminate the carrier state. It was "extremely well tolerated in all 191 individuals who received it either prophylactically or therapeutically."

Galoota, W. B., and Moranville, B. A.: *Student Medicine* (in press)

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS

EATON LABORATORIES, NORWICH, NEW YORK

Please Mention this Journal when writing to Advertisers



**NOW...**

**FOR ADULTS -  
CHILDREN - INFANTS**

A CONTRAST MEDIUM THAT  
FULFILLS ALL THE  
CRITERIA FOR  
RADIOLOGIC EXAMINATION  
OF THE  
ALIMENTARY CANAL



**GASTROGRAFIN**

Squibb Contrast Medium for Gastrointestinal Roentgenography

- \* *a true solution*—permits delineation of gastric and duodenal mucosa, and identification of small ulcers
- \* *does not inspissate*—risk of residual hard masses eliminated; safe for use in the acutely ill and in cases of suspected or known obstruction
- \* *minimal absorption*—passes readily along alimentary tract with negligible absorption
- \* *virtually nontoxic*—safe on accidental, or deliberate, introduction into body cavities; may be used in post-anastomosis studies
- \* *miscible with blood*—allows detection of bleeding points and visualization of bleeding ulcers
- \* *low viscosity*—permits demonstration of small fistulous connections, including tracheoesophageal fistulae in infants
- \* *cathartic effect*—eliminates delay in surgical procedures, or in serial or follow-up radiologic studies
- \* *well tolerated*—side reactions minimal; contraindicated only in individuals with iodine sensitivity
- \* *may be administered orally, by tube, or by rectum*

*Gastrografin*, providing 76% sodium and methylglucamine diacetylaminotriiodobenzoates, is supplied in bottles of 120 cc. (4 fl. oz.).

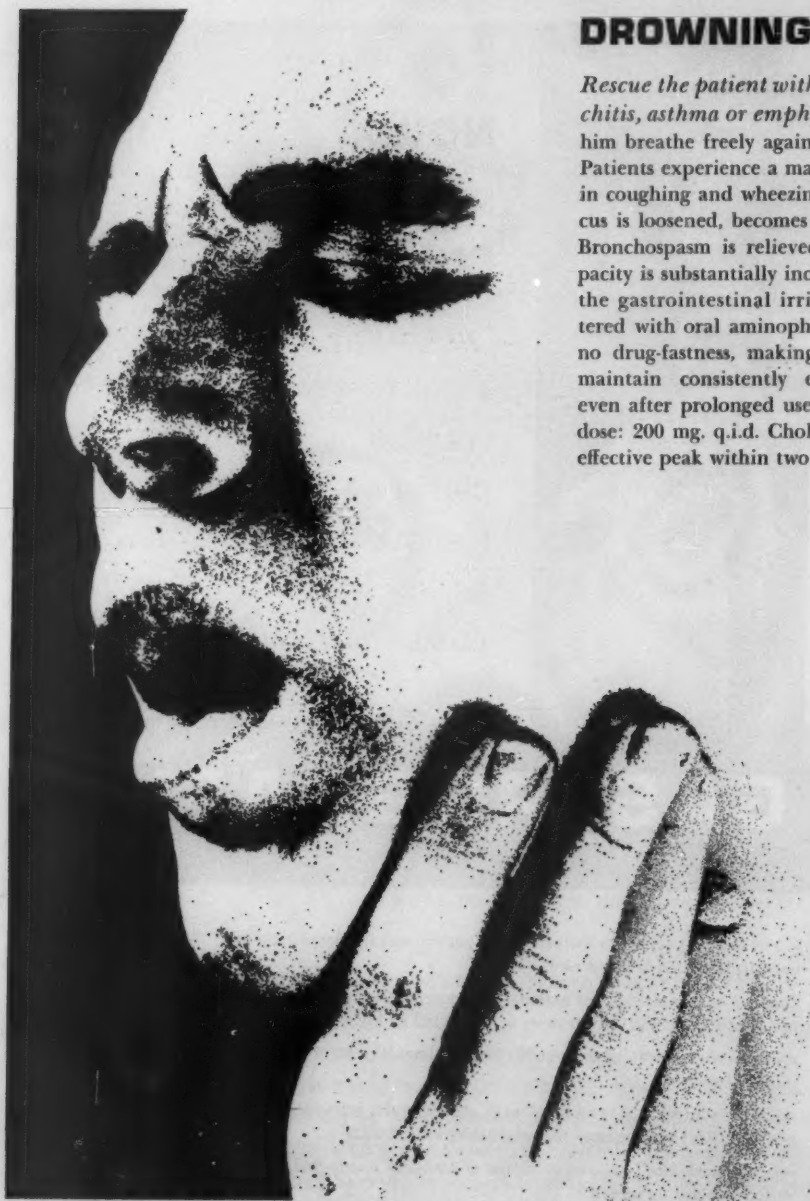
**SQUIBB**

New York 22, N. Y.



*Squibb Quality—  
The Priceless Ingredient*

"GASTROGRAFIN" IS A SQUIBB TRADEMARK



## DROWNING IN AIR

*Rescue the patient with chronic bronchitis, asthma or emphysema and help him breathe freely again with Cholearyl. Patients experience a marked abatement in coughing and wheezing . . . thick mucus is loosened, becomes easier to expel. Bronchospasm is relieved, and vital capacity is substantially increased—without the gastrointestinal irritation encountered with oral aminophylline. There is no drug-fastness, making it possible to maintain consistently effective results even after prolonged use. Average adult dose: 200 mg. q.i.d. Cholearyl reaches an effective peak within two weeks.*

*better breathing . . . forestalls the crisis*

# CHOLEARYL®

brand of oxtriphylline



## In skeletal-muscle disabilities . . .

### Curbs spasm, relieves rigidity, and relaxes psychic tension

Of all muscle relaxants in current use, only meprobamate is supported by hundreds of published clinical studies that demonstrate relaxing action on both the brain and the skeletal musculature. EQUANIL reduces muscular spasm and tension, aids in the restoration of mobility, speeds rehabilitation, lessens the emotional overlay.

*Prescribe it in spasm or tension secondary to: sprains, strains, contractures, fibrositis, myositis, low-back syndrome, frozen shoulder, cervical-rib syndrome, herniated intervertebral disk, wryneck, rheumatoid arthritis, rheumatoid or traumatic spondylitis, certain neuromuscular disorders.*

# Equanil<sup>®</sup>

Meprobamate,

Wyeth



Philadelphia 1, Pa.



# L. A.\* FORMULA\*

in ORANGE JUICE  
or other citrus juices



in MILK  
so pleasant tasting



in WATER  
easy to take



*the truly palatable*

## bowel NORMALIZER

*to provide your patients with the smooth bulk so essential to normal bowel function*

L. A. FORMULA substitutes a moist smooth bulk for the fibrous, irritating bulk of uncertain consistency which results from the average diet. L. A. FORMULA disperses intimately with the intestinal contents to form a softly compact, well-formed stool of normal consistency which clears the rectum completely and easily.

\*Abbreviation for the Latin "Levis Amplitudo", meaning smooth bulk.

\*Refined psyllium hydrophilic mucilloid with lactose and dextrose.



*Your Patients  
will appreciate  
the modest cost!*

SAMPLES AVAILABLE PROMPTLY UPON REQUEST

Made by BURTON, PARSONS & COMPANY, Since 1932  
Originators of Fine Hydrophilic Colloids  
Washington 9, D. C.

# dust a major offender

Dust is a principal offender in allergies of the respiratory tract. It cannot be avoided — and the dust-allergic patient requires medical attention. POLARAMINE — the closest to a perfect antihistamine — is the closest to a perfect solution for the problem of the patient suffering from irritating nonseasonal allergens. POLARAMINE offers swift, sure, safe action with these outstanding advantages —

- Therapeutically effective at lower dosages than other antihistamines
- Highest therapeutic index of all antihistamines (3380)
- Fewer side effects than with other antihistamine preparations
- Highly efficacious — a single POLARAMINE REPETAB gives your patient all-day or all-night protection from discomfort of allergic symptoms

## POLARAMINE REPETABS

SUPPLY: POLARAMINE REPETABS, 6 mg., bottles of 100 and 1000 / POLARAMINE REPETABS, 4 mg., bottles of 100 and 1000 / Tablets, 2 mg., bottles of 100 and 1000 / Polaramine Syrup, 2 mg./5 cc., bottles of 16 oz.

SCHERING CORPORATION • BLOOMFIELD, N.J.



symbol of the  
one-dose  
convenience  
you want for  
your patient

Schering

EN-1482-S

POLARAMINE

brand of tetra-chloropheniramine maleate. REPETABS® Repeat Action Tablets.

# NOW even many cardiac patients may have THE FULL BENEFITS OF CORTICOSTEROID THERAPY

**DECADRON**—the new and most potent of all corticosteroids, eliminated fluid retention in all but 0.3 percent of 1500 patients†, and induced beneficial diuresis in nearly all cases of pre-existing edema.



**Decadron** \*  
DEXAMETHASONE  
treats more patients  
more effectively

Therapy with DECADRON has also been distinguished by virtual absence of diabetogenic effects and hypertension, by fewer and milder Cushingoid reactions, and by freedom from any new or "peculiar" side effects. Moreover, DECADRON has helped restore a "natural" sense of well-being.

†Analysis of clinical reports.

\*DECADRON is a trademark of Merck & Co., Inc., ©1958 Merck & Co., Inc.



**MERCK SHARP & DOHME**  
Division of Merck & Co., Inc., Philadelphia 1, Pa.

# ANNALS OF INTERNAL MEDICINE

---

VOLUME 51

NOVEMBER, 1959

NUMBER 5

---

## CONCERNING THE FUNCTIONS AND NOMENCLATURE OF BLOOD CLOTTING FACTORS, WITH A PRELIMINARY REPORT OF THE PROFILE OF BLOOD CLOTTING FACTORS IN YOUNG MALES \*†

By IRVING S. WRIGHT, M.D., F.A.C.P., *New York, N. Y.*

DURING the last decade it became increasingly apparent that those who were exploring for new knowledge about blood clotting had created a Tower of Babel, and that new stories were constantly being added to that Tower. Workers in the field were able to communicate only with the greatest difficulty. The general clinician and the student found the literature to be a maze worthy of the Minoans. Two of the blood clotting factors were described by 13 different terms and a third by 12; one factor had been given four different names by a single investigator.

This problem was recognized as serious at the First International Congress of Thrombosis and Embolism, held, in Basel in 1954, and the International Committee for the Standardization of the Nomenclature of Blood Clotting Factors was established.<sup>1</sup> Twenty-two members from 15 countries were appointed. The list included most of the leading workers in the field, and the majority of the factors recently recognized had been discovered by these gentlemen. It was felt that the task of obtaining agreement on a common nomenclature was almost insurmountable, and that, without the coöperation of this group, many of whom had paternal pride in the names,

\* Received for publication May 16, 1959.

Presented at the Fortieth Annual Session of The American College of Physicians, Chicago, Illinois, April 22, 1959.

From the Department of Medicine, The New York Hospital-Cornell Medical Center, New York, N. Y.

† Aided by grants from the National Heart Institute, Lasker Foundation and the Lillia Babbit Hyde Foundation.

Requests for reprints should be addressed to Irving S. Wright, M.D., Professor of Clinical Medicine, The New York Hospital-Cornell Medical Center, 525 E. 68 St., New York, N. Y.

---

Copyright ©, 1959, by The American College of Physicians

it would never be widely accepted. Nevertheless, it was recognized that those who created this confusion had a moral and scientific responsibility to unravel it. I was asked to serve as Chairman, probably because I had never described a new factor and had no vested interest in any particular name or system of nomenclature. Since then, meetings have been held in

TABLE 1  
Nomenclature of Blood Clotting Factors

- I Fibrinogen
- II Prothrombin
- III Thromboplastins
  - (a) Lung
  - (b) Brain
  - (c) Platelet
  - (d) Other tissues
- IV Calcium
- V Factor V (Owren)
  - Proaccelerin (Owren)
  - Labile Factor (Quick)
  - Plasma Ac-globulin (Ware and Seegers)
  - Thrombogene (Nolf)
  - Prothrombinase (Owren)
  - Prothrombinokinase (Milstone)
  - PPCF—Plasmin Prothrombins—Conversion Factor (Stefanini)
  - Component A of Prothrombin (Quick)
  - Prothrombin Accelerator (Fantl and Nance)
  - Co-Factor of Thromboplastin (Honorato)
- VII Factor VII (Koller)
  - Proconvertin (Owren)
  - SPCA—Serum Prothrombin Conversion Accelerator (deVries, Alexander)
  - Stabile Factor (Stefanini)
  - Cofactor V (Owren)
  - Serozym (Bordet)
  - Kappa Factor (Sorbye and Dam)
  - Prothrombinogen ? (Quick)
  - Co-Thromboplastin (Mann and Hurn)
  - Serum Accelerator (Jacox)
  - Prothrombin Conversion Factor (Owren)
  - Prothrombin Converting Factor (Jacox)
- VIII Factor VIII (Koller)
  - Antihemophilic Globulin (Patek and Taylor)
  - Antihemophilic Globulin A (Cramer)
  - AHF—Antihemophilic Factor (Brinkhous)
  - PTF—Plasma Thromboplastic Factor (Ratnoff)
  - Plasma Thromboplastic Factor A (Aggeler)
  - TPC—Thromboplastic Plasma Component (Shinowara)
  - Facteur Antihemophilique A (Soulier)
  - Thromboplastinogen (Quick)
  - Prothrombokinase (Feissly)
  - Platelet Cofactor (Johnson)
  - Plasmokinin (Laki)
  - Thrombokatilysin (Lenggenhager)
- IX Christmas Factor (Biggs and MacFarlane)
  - Factor IX (Koller)
  - PTC—Plasma Thromboplastic Component (Aggeler)
  - Antihemophilic Globulin B (Cramer)
  - Plasma Thromboplastic Factor B (Aggeler)
  - Plasma Factor X (Shulman)
  - Facteur Antihemophilique B (Soulier)

Boston, Oxford, Copenhagen and Rome, with continuing activity in numerous laboratories during the interim. Basic agreements were reached on the following points:

1. The situation was chaotic, and some system of universal names or symbols was essential to permit further progress in communication and teaching in this field.
2. The development of any such system would necessitate the yielding of some of the pride of authorship for the common good.
3. The new system should avoid names which imply an action by the factor. The reason for this had become clear when factors which had previously been given names implying function had later proved not to have that function, but rather quite a different one.
4. The symbols or names used should convey the same meaning in any language.

As time passed it became increasingly evident that only a numerical system fully met these qualifications, and since some of the factors had already received Roman numerals in addition to other names, this seemed a logical point from which to start discussion. In September, 1958, in Rome, it was finally and quite appropriately agreed that Roman numerals should be used as the International Symbolic Code, and that following the symbol the author could, if he so desired, include whatever synonym he wished. This should be in parentheses. Thus, one would write factor V (proaccelerin), or, if one wished, factor V (labile factor). The Roman numeral would be intelligible in any language, including the Oriental and more exotic languages. Arabic numerals were reserved for platelet factors. These have not as yet been officially assigned, although some are in common usage.

The first four factors are so widely known by their names that the Roman numerals seem less necessary, but may be used. Thus: I—Fibrinogen; II—Prothrombin; III—Thromboplastins; IV—Calcium. It seems likely that, for these, the names will continue in common usage.

It will be noted that "thromboplastins" is plural, because they may develop from many sources, and due recognition is given to this. If a subdivision is desired, small letters will be used to indicate the source; e.g.:

III—thromboplastins

- (a) lung
- (b) brain
- (c) platelets
- (d) other tissues

Thus—III(a) or III(c).

The principle having been established, it was then essential to develop criteria by which one could establish the actual existence of a factor, and

to determine which factors were at present sufficiently well identified to justify being assigned a number. This task was assigned to a Criterion Committee, with Professor Robert Hunter, of Dundee, as Chairman. The details of the studies cannot be elaborated here, but the broad points of agreement for the operation of this committee were as follows:

1. The minimal requirements for the characterization of a clotting factor in whole blood, plasma or serum shall be reproducible data regarding the effect of storage, absorbability, inactivation by heating, and the effect of changes in the pH. Additional chemical data are desirable if available.
2. Any clinically identifiable state associated with an abnormality in the clotting mechanism shall be regarded as supporting the evidence for the lack or excess of a factor.
3. It is essential to list methods of assay of physiologic properties, an appropriate selection of which methods will be considered as minimal for presentation of a factor before the Criterion Committee. In case of previously undescribed factors, the mechanism used for identification shall be clearly described by the author and considered acceptable by the Committee.

With the use of these criteria, the following factors have been exhaustively studied and assigned permanent symbols:

*Factor V*: Deficiency of this factor results in a hemorrhagic diathesis which is probably inherited and has been described as a parahemophilia or hypopro-accelerinemia. The first case was recognized and described by Owren<sup>2</sup> in a beautiful study carried on under the most adverse conditions due to the Nazi occupation of Norway, while Dr. Owren was at the same time an active member of the underground resistance. Several additional cases have since been described. This factor seems necessary for the formation of the prothrombin-converting substance in the blood and in tissue extracts. The details of the biochemistry, preparation and assay of the different factors are not within the scope of this paper.<sup>3,4,5</sup>

*Factor VII* plays a part in the production of at least three groups of abnormal states, as follows: (1) A congenital deficiency may produce hemorrhagic phenomena, with purpura and bleeding from the mucous membranes. Many such cases have been described. (2) Acquired deficiency may occur in liver disease, in vitamin K deficiency, in the immediate neonatal period, and following the administration of prothrombinopenic agents, such as the coumarin derivatives used in anticoagulant therapy. (3) Excesses of Factor VII have been found in certain states associated with a high incidence of thrombo-embolism, such as the third trimester of pregnancy. The level of this substance in the blood is species-specific. Deficiency results in a quantitative prolongation of the one-stage prothrombin to thrombin in the presence of tissue thromboplastin, Factor V and  $\text{Ca}^{++}$ .

It does not accelerate the interaction of platelet Factor 3 and Factors VIII and IX. It cannot rectify Factor V deficiency-retarded coagulation. It is not essential for thromboplastin generation in the coagulating blood. Other interesting properties are fully described in the literature.<sup>6, 7, 8, 9, 10</sup>

*Factor VIII* deficiency represents the classic hemophilia A, which is well known as the hereditary hemorrhagic disease that occurs almost exclusively in males but that is female sex-linked. The degree of Factor VIII deficiency varies from patient to patient. Hemorrhage occurs in any tissues following minor injuries, and is frequently very serious. Factor VIII enters into the early stages of coagulation with Factor IX and  $\text{Ca}^{++}$  to produce an intermediate product which reacts with platelet Factor 3. The result of this reaction in the presence of Factor V is a very active agent in prothrombin conversion. It is essential in the formation of blood thromboplastin. A deficiency (1) prolongs the clotting time; (2) diminishes the thromboplastin formed, and (3) diminishes the prothrombin conversion.<sup>11, 12</sup>

*Factor IX* deficiency produces hemophilia B, or Christmas disease, named after the now famous patient of Biggs and MacFarlane. This is usually a severe hemorrhagic disorder, resembling hemophilia A and inherited in the same way. Studies of this disorder led to the discovery of Factor IX. Factor IX, like Factor VIII, is essential for the formation of intrinsic blood thromboplastin. It probably enters into reactions leading to the formation of this thromboplastin, forming with  $\text{Ca}^{++}$  and Factor VIII an intermediate product which then reacts with platelet Factor 3 and Factor V. It influences primarily the amount of thromboplastin formed and not the rate of its generation.<sup>13, 14</sup>

A brief report of the above findings of the Committee will shortly appear in leading medical journals in many countries.

#### NEW FACTORS UNDER CONSIDERATION

A number of additional plasma and serum factors have been described by various workers who believe they have established that these play a role in blood clotting. These factors are now under study by the Committee, and if the evidence indicates that the claims are valid they will be assigned Roman numerals.

A factor unofficially termed Factor X by F. Koller<sup>15</sup> has been studied. He considers that this has been demonstrated by tests with mixtures of various sera in the thromboplastin generation test. Serum of a patient receiving Dicumarol, for example, produces a marked delay of thromboplastin generation, even if Factor VII has been brought to normal by administration of vitamin K<sub>1</sub>. Similarly, serum from a patient with deficiency of Factor IX (Christmas) also shows a delayed thromboplastin generation. Mixture of the two sera, however, produces normalization. Koller has therefore concluded that the Dicumarol serum is lacking a factor other than Factor VII or IX. Serum of a newborn or of a patient suffering from hepatitis

or cirrhosis may behave in the same way. Stored serum gradually becomes deficient in this factor before the concentration of Factor VII or IX decreases. This evidence, while suggestive, has not generally been accepted as conclusive, and therefore, pending further work, the Committee has deferred adopting the symbol of Factor X.

Among the most firmly established is the so-called Stuart Factor, named after a patient of Hougie, Barrow and Graham<sup>16, 17</sup> in Chapel Hill. Deficiency of this factor results in hemorrhage, such as epistaxis, hemarthrosis and hematomata. At times the bleeding can produce an anemia severe enough to require transfusion. Patient Stuart had five children at the last report, all of whom showed a definite decrease in Stuart Factor, ranging from 52 to 21% of normal. The deficiency was inherited as a highly penetrant but incompletely recessive autosomal characteristic. Plasma with lack of Stuart Factor gives a long prothrombin time in the presence of tissue thromboplastin, defective thromboplastin generation, a long partial thromboplastin time, a long recalcified clotting time and impaired prothrombin utilization. Russell's viper venom fails to correct the abnormal prothrombin time defect. A meeting of the Committee was held in Montreux, Switzerland, in August, 1959, to consider all evidence regarding this and other new factors. If the evidence concerning the Stuart Factor is held to be sufficient, it may be assigned either Roman numeral VI or X.\*

A deficiency of plasma thromboplastin antecedent (PTA) was described by Rosenthal, Dreskin and Rosenthal in 1953.<sup>18</sup> It is believed to produce a mild hemorrhagic bleeding tendency, thought to be due to lack of a specific factor (PTA) necessary for blood coagulation and hemostasis. The term "Hemophilia C" has been used as a synonym. The bleeding is less severe than that with Hemophilia A or B. The deficiency gives an abnormally short serum prothrombin time, a long partial thromboplastin time, and incomplete thromboplastin generation. The prothrombin time, platelet number, bleeding time and capillary fragility are not influenced by absence of this factor. It has been suggested that this actually represents multiple mild deficiencies of other coagulation factors, for example, Factors VIII and IX. This problem will be investigated further by the Committee.

Another factor under consideration is the Hageman Factor, named after the first patient of Ratnoff and Colopy.<sup>19, 20</sup> This factor is thought to be necessary for *in vitro* blood coagulation. Patients with a deficiency of this factor have no symptoms or bleeding tendency. This is known at present as the Hageman trait. A few patients with this trait have been discovered as a result of routine coagulation studies done prior to anticipated surgical procedures. While these patients have abnormal coagulation studies, they do not develop unusual hemorrhagic complications following surgery or accidental trauma. The clotting time of whole blood is usually abnormally long in either plain glass or siliconized tubes. The recalcified clotting time

\* At this meeting it was decided that the Stuart-Prower Factor was similar in many respects to Factor X as described by Koller. The committee therefore assigned the Roman X to designate the Stuart-Prower Factor.

of the plasma, the serum prothrombin time, thromboplastin generation and partial thromboplastin time are also abnormal in patients with this defect. Prothrombin time is usually normal but may be slightly prolonged. Bleeding time, fibrinogen and capillary fragility are not affected.

Deficiency of the Hageman Factor has not been found in any parent or offspring of a patient with such a deficiency. Two sisters have been studied who have this deficiency, but no other members of their family were found to have it. Ratnoff and Margolis believe that this is transmitted as an autosomal recessive trait.

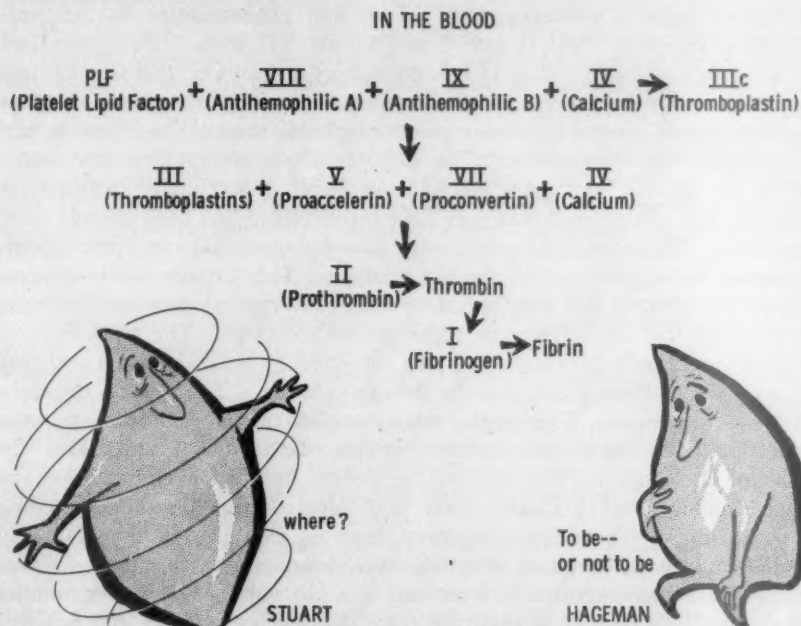


FIG. 1. One way of presenting a present theory of clotting.

Whether this should be listed as a blood clotting factor is still a matter for debate, since no hemorrhagic disease is associated with this deficiency and it has therefore been demonstrated to exist only *in vitro*. Its significance in the mechanism of blood clotting *in vivo* remains an open question.

#### CLOTTING FACTORS IN NORMAL YOUNG MALES

During the last year we have embarked on a study to determine the incidence of abnormalities of the blood clotting mechanism present in so-called normal young males. Margaret Todd, Ph.D., of our laboratory, has been responsible for the chemical studies. For this purpose we have used the following tests for screening purposes:

Glass and silicone clotting times, prothrombin complex, prothrombin consumption, partial thromboplastin tests, heparin tolerance, and recalcification times, prothrombin and proconvertin tests, tests for Factor V (ac-globulin), Factor VII (proconvertin), Factor II (prothrombin), Stuart-Prower Factor and antithrombin titers.

At the time of this writing, these studies have been conducted on 106 Cornell University male medical students, age 22 to 30 years. As expected, most of them have been normal, but we were surprised to find that 18 (or 16%) showed some abnormalities. Eleven (or 10%) had abnormally shortened heparin tolerance tests. Two had abnormalities in the prothrombin complex, P&P (Owren) and Factor VII tests. Two more had persistently prolonged Factor II (prothrombin) times. One had an abnormal fibrinolysis, which was complete in about one hour in glass tubes. The first student studied proved to be most interesting. He showed the following unusual pattern of abnormalities: The Lee-White coagulation time was markedly prolonged in both glass and silicone-treated tubes. The prothrombin consumption test showed that very little prothrombin had been utilized after one hour. The partial thromboplastin time demonstrated very little thromboplastin to be generated by the test plasmas. The thromboplastin generation test confirmed this and, by substitution of normal plasma and serum, it was shown that the defect was in the patient's plasma. The recalcification time was markedly prolonged but was corrected by normal plasma and that of a known antihemophilic globulin-deficient plasma. The heparin tolerance test was prolonged. The prothrombin complex time was normal, as were all of the individual factors concerned in this mixture (II, V and VII). In spite of these marked deficiencies, the patient has had a circumcision, an appendectomy, and a tonsillectomy and adenoidectomy without bleeding complications. There have, however, been no examples of the Hageman trait in which parents and offspring have demonstrated this trait. (Two sisters have been reported to have had it.) In our case, however, studies of the patient's mother showed the same deficiencies, and she too has had surgery without hemorrhagic complications. His father is entirely normal in all respects. Further studies suggest this student's trait is closer to P.T.A. (Rosenthal) deficiency but this has not been entirely accepted as yet. This case will be reported in detail at a later date.

If an incidence of approximately 16% should persist as the size of the series is enlarged, this will constitute a significant pattern of deficiency in the population which should be more completely understood and will require further investigation. The significance of such findings in the long-range history of the individual will be of considerable interest.

#### SUMMARY

This report represents an effort to condense and clarify the present status of studies concerning factors which occur in the plasma and serum and

which play significant roles in the clotting of the blood. No attempt has been made to include an analysis of platelet factors. This is a matter for further evaluation.

A preliminary report is included of the results of a survey of the profiles of the clotting factors of 106 so-called normal young males. It was found that 16% showed some abnormality at the time of testing. This study is being enlarged and is part of a long-term project. Other sex and age groups will be included.

#### SUMMARY IN INTERLINGUA

In le curso del passate decennio, nove factores de coagulation sanguinee, non previelemente recognoscite, ha essite descripte e studiate in numerose laboratorios in omne partes del mundo. Pro plures de istos, varie recercatores proponeva nomines de selection personal. Le resultado esseva un serie grado de confusion in le litteratura, lo que ha grandemente impedito le libere fluxo del communication e le docentia in iste campo. Plure factores ha essite designate per 12 nomines o plus.

Le Committee International pro le Standardisation del Nomenclatura del Factores de Coagulation Sanguinee esseva establite in 1954. Iste committee ha convenite in le curso del annos depost su establimento e ha effectuate un accordo con respecto al uso de un systema international in que le numerales roman servi como symbolos primari pro le varie factores. Si le autor lo desiro, ille pote adder le appropriate synonymo de su selection personal. Un tabula del symbolos e del synonymos es includite in le corpore del presente articulo. Symbolos esseva officialmente establite pro le Factores I, II, III, IV, V, VII, VIII, e IX, post que le committee se habeva ponite de accordo que le existentia e le functiones del correspondent factoros esseva sufficientemente ben establite pro justificar le ascription de symbolos definitive a illos. Factores additional es sub investigation per un sub-committee. Istos include le factor Stuart-Prower, le antecedente de thromboplastina plasmatic (PTA), le factor Hageman, e le factor X (Koller). Si o non iste factores va recipere symbolos international depende del fortia de conviction del datos adducite pro establir lor existentia e lor activitate.

Es includite un reporto preliminar con respecto al incidentia de anormalitates trovate in 106 normal juvene masculos (studentes de medicina) qui esseva studiate per varie tests pro le mecanismo e le factores de coagulation sanguinee. Esseva trovate que circa 16% de iste si-appellate normales exhibiva certe anormalitates in lor mecanismo del coagulation del sanguine al tempore del tests. Le ultime signification de iste constatacion con respecto al incidentia de complicationes thromboembolic e hemorrhagic e al longevitate va esser le thema de un studio a longe vista in tanto que iste studentes va esser tenite sub observation a transverso lor vitas futur.

#### BIBLIOGRAPHY

1. Thrombosis and embolism, Proceedings of the First International Conference, 1954, Benno Schwabe & Co., Basel, p. 1209.
2. Owren, P. A.: The coagulation of the blood, 1947, Gunderson, Oslo.
3. Fahey, J., Ware, A. G., and Seegers, W. H.: Stability of prothrombin and Ac-globulin in stored human plasma as influenced by conditions of storage, *Am. J. Physiol.* **154**: 122, 1948.
4. Stefanini, M.: Studies on the role of calcium in the coagulation of blood, *Acta med. Scandinav.* **136**: 250, 1950.
5. Soulier, J. P., and Larrieu, M. J.: Differentiation of hemophilia into two groups (a study of 33 cases), *New England J. Med.* **249**: 547, 1953.

6. (a) Owren, P. A.: The diagnosis and prognostic significance of plasma prothrombin and Factor V levels in parenchymatous hepatitis and obstructive jaundice, *Scandinav. J. Clin. and Lab. Invest.* **1**: 131, 1949.
- (b) Owren, P. A., and Bjerkehlund, C.: A new previously unknown clotting factor, *Scandinav. J. Clin. and Lab. Invest.* **1**: 162-163, 1949.
7. Conley, C. L., Hartmann, R. C., and Morse, W. I.: The clotting behavior of human "platelet-free" plasma: evidence for the existence of a "plasma thromboplastin," *J. Clin. Investigation* **28**: 340, 1948.
8. Stefanini, M.: Mechanism of blood coagulation in normal and pathologic conditions, *Am. J. Med.* **14**: 64, 1953.
9. Alexander, B., Goldstein, R., and Landwehr, G.: The prothrombin conversion accelerator of serum (SPCA): its partial purification and its properties compared with serum Ac-globulin, *J. Clin. Investigation* **29**: 881, 1950.
10. Owren, P. A., and McKenzie, B. F.: Application of paper electrophoresis to separation of blood clotting factors, *J. Appl. Physiol.* **6**: 696, 1954.
11. Tocantins, L. M.: The coagulation of the blood, 1955, Grune & Stratton, New York.
12. Biggs, R., and MacFarlane, R. G.: Human blood coagulation and its disorders, 1957, Charles C Thomas, Springfield, Illinois.
13. Aggeler, P. M., White, S. G., Glendening, M. B., Page, E. W., Leake, T. B., and Bates, G.: Plasma thromboplastin component (PTC) deficiency: a new disease resembling hemophilia, *Proc. Soc. Exper. Biol. and Med.* **79**: 692, 1952.
14. Biggs, R., Douglas, A. S., MacFarlane, R. G., Dacie, J. V., Pitney, W. R., Merskey, C., and O'Brien, J. R.: Christmas disease: a condition previously mistaken for haemophilia, *Brit. M. J.* **2**: 1398, 1952.
15. Koller, F.: Thrombosis and embolism, in *Proceedings of the First International Conference, 1954*, Benno Schwabe & Co., Basel, p. 1206.
16. Hougie, C., Barrow, E. M., and Graham, J. B.: Stuart clotting defect. I. Segregation of an hereditary hemorrhagic state from the heterogeneous group heretofore called "stabile factor" (SPCA, proconvertin, Factor VII), *J. Clin. Investigation* **36**: 485, 1957.
17. Graham, J. B., Barrow, E. M., and Hougie, C.: Stuart clotting defect. II. Genetic aspects of a new hemorrhagic state, *J. Clin. Investigation* **36**: 497, 1957.
18. Rosenthal, R. L., Dreskin, O. H., and Rosenthal, N.: New hemophilia-like disease caused by deficiency of a third plasma thrombo-factor, *Proc. Soc. Exper. Biol. and Med.* **82**: 171, 1953.
19. Ratnoff, O. D., and Colopy, J. E.: A familial hemorrhagic trait associated with a deficiency of a clot-promoting fraction of plasma, *J. Clin. Investigation* **34**: 602, 1955.
20. Ratnoff, O. D.: A familial trait characterized by deficiency of a clot-promoting fraction of plasma, *J. Lab. and Clin. Med.* **44**: 915, 1954.

## STUDIES OF POSTSTREPTOCOCCAL NEPHRITIS AND OTHER GLOMERULAR DISEASES \* †

By DAVID P. EARLE, M.D., F.A.C.P., and ROBERT B. JENNINGS, M.D.,  
*Chicago, Illinois*

UNCERTAINTIES and disagreements still complicate consideration of diseases that affect primarily the glomerulus. Although specific therapy is not at hand, accurate classification and clear concepts of the natural histories of these diseases contribute significantly to their understanding, practical clinical management and prognosis.

The keystone of our approach to this problem is a correlation of the clinical course with serial histologic observations in 36 adults with sporadic acute glomerulonephritis whose disease followed *proved* hemolytic streptococcal infection (table 1). Recovery of group A hemolytic streptococci on culture, and/or a significant increase in serum antistreptolysin, antistreptokinase or antihyaluronidase titers on serial measurements, were required in all patients included in this group. In addition, serum antibodies against Type 12 streptococcus, which has been shown by Rammelkamp<sup>1</sup> and others<sup>2</sup> to be commonly associated with acute nephritis, were demonstrated in 10 of these 36 patients. Fortunately, the pathologic findings in these patients are quite characteristic. We believe that these patients represent a clear-cut specific disease entity that corresponds to Longcope's Type A<sup>3</sup> or Ellis' Type 1<sup>4</sup> nephritis. An understanding of the course of events in these patients should furnish a good foundation for the consideration of other glomerular disease of nonstreptococcal origin.

Our concept of the natural history of poststreptococcal glomerulonephritis is shown in figure 1.<sup>5,6</sup> Acute glomerulonephritis develops several weeks after a streptococcal infection. Some cases of nephritis are so mild that they can be detected only by careful serial examinations of the urine. In a few patients the disease is severe enough to cause death in the acute phase, or it becomes progressive, with death in a year or so. However, the majority of patients soon improve, and many heal completely. Second attacks

\* Received for publication May 16, 1959.

Presented at the Fortieth Annual Session of the American College of Physicians, Chicago, Illinois, April 21, 1959.

From the Departments of Medicine and Pathology, Northwestern University Medical School, and the Departments of Medicine, Veterans Administration Research Hospital and Passavant Memorial Hospital, Chicago, Illinois, and U. S. Naval Hospital, Great Lakes, Illinois.

† Supported in part by grants from the National Heart Institute, National Institutes of Health, U. S. Public Health Service (H-1815 and H-1890), and the Otho S. A. Sprague Foundation.

Views expressed are those of the authors and do not necessarily reflect the opinion of the Navy Department or the Veterans Administration.

Requests for reprints should be addressed to David P. Earle, M.D., 303 East Chicago Avenue, Chicago 11, Illinois.

TABLE 1  
Our Series of Proved Poststreptococcal Acute Glomerulonephritis

	Number of Patients
Acute glomerulonephritis→Healed	16
Acute glomerulonephritis→Chronic	16
Acute glomerulonephritis→Death	1
Four exacerbations in chronic glomerulonephritis	3
Total	36

are extremely rare among healed patients, even after proved streptococcal infections.<sup>7</sup> The remaining patients, despite improvement, continue to have proteinuria, and are classified as chronic latent glomerulonephritis. Exacerbations very similar to the initial acute attack occur in approximately 20% of these, and usually follow another streptococcal infection.<sup>8</sup> Whether or not exacerbations develop, renal function gradually deteriorates, causing uremia and death after five to 30 years.<sup>9</sup> Some patients develop the nephrotic syndrome,<sup>10</sup> but this should not be considered to be an exacerbation in the true sense. However, all instances of the nephrotic syndrome or of clinical chronic nephritis *do not* necessarily represent poststreptococcal chronic glomerulonephritis.

A typical glomerulus from a biopsy obtained one month after onset of a severe poststreptococcal acute nephritis is shown in figure 2. A 40 year old man developed gross hematuria, edema, hypertension and moderate

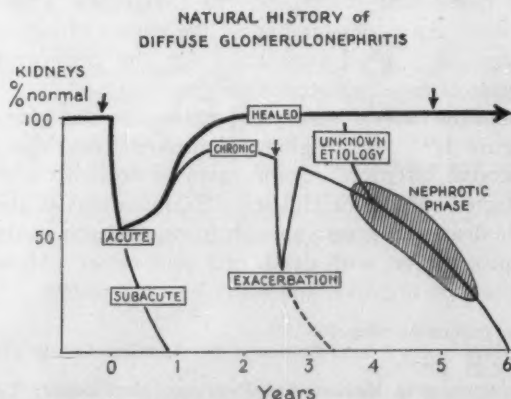


FIG. 1. Natural history of diffuse glomerulonephritis. Time is indicated by the abscissa of the figure, while the status of the kidneys is shown by the ordinate, 100% indicating normal kidneys. The degree of kidney disease represented by various percentages less than 100 is not intended to be quantitatively precise, nor is the time factor meant to be absolute. The arrows indicate Group A hemolytic streptococcal infections. The dashed line below exacerbation indicates that a small number of exacerbations are followed by rapid progression of renal functional impairment, perhaps analogous to the relatively uncommon subacute course subsequent to an initial attack of acute glomerulonephritis. (Courtesy "Disease-a-Month," The Year Book Publishers, Chicago, Illinois.)

nitrogen retention 12 days after a proved streptococcal pharyngitis. Considerable hypercellularity is apparent, due chiefly to endothelial cell proliferation with some leukocytic infiltration. All of 28 glomeruli obtained from this patient were similarly involved, but no other abnormalities were found in four biopsies. His urine became normal three months after onset, and three subsequent biopsies revealed gradual subsidence of the hypercellularity (figure 3), although some was still present two years after disappearance of proteinuria.

More serious glomerular damage is found in those who fail to heal (figure 4). This 37 year old woman developed proteinuria, microscopic

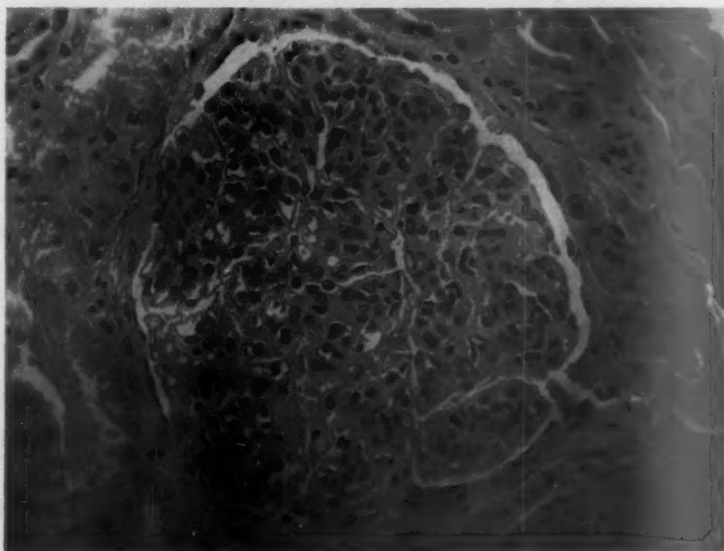


FIG. 2. Glomerulus from patient Ser. with poststreptococcal acute glomerulonephritis, 30 days after onset. This patient's nephritis healed 90 days after onset, and 60 days after this biopsy. Note the hypercellularity, which is diffuse throughout the glomerulus and is due to an increase of cells within the capillary loops. Inspection under higher power reveals approximately 10 polymorphonuclear neutrophils in the capillaries of each lobule. (Fixed in Helly's fluid, 2 $\mu$  section, H&E, 400  $\times$ .)

hematuria, edema and hypertension 12 days after a proved streptococcal sinusitis. The blood urea nitrogen increased to 79 mg. per 100 ml. Glomerular hypercellularity due to endothelial cell proliferation and the presence of many polymorphonuclear neutrophils were noted in all glomeruli in this biopsy, obtained three weeks after onset. In addition, more serious glomerular damage, as evidenced by crescents, adhesions and foci of necrosis of glomerular lobules, was observed in six of the 15 glomeruli in this biopsy. Edema and diffuse early interstitial fibrosis also were apparent. Hypertension persisted for 10 months, renal function has not yet returned to

normal, and proteinuria is still present two years after onset. Two subsequent biopsies have shown persistence of chronic glomerulonephritis with marked diffuse interstitial fibrosis (figure 5).

Certain clinical features in 32 adult patients with proved poststreptococcal acute nephritis are shown in table 2. Sixteen patients healed clinically, as evidenced by permanent disappearance of proteinuria, while 16 improved but did not heal. Not included in this analysis are one patient who died in the acute phase and four poststreptococcal exacerbations in three patients with chronic glomerulonephritis. Half of each group had gross hematuria. However, a greater incidence of edema, hypertension and defi-

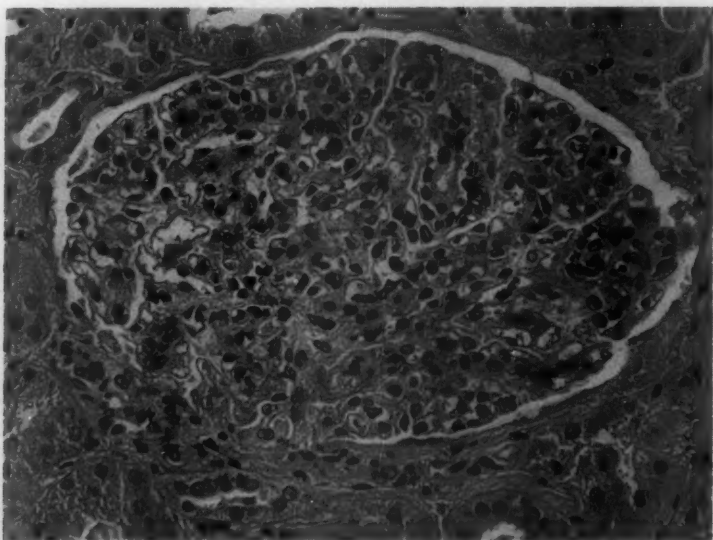


FIG. 3. Glomerulus from same patient as figure 2, 66 days after disappearance of proteinuria and 126 days after the first biopsy. Note that the glomerulus is still hypercellular, but less so than in the first biopsy. The hypercellularity is localized in the lobular stalks of the glomeruli. (Fixed in Helly's fluid, 2 $\mu$  section, H&E, 400 $\times$ .)

nite nitrogen retention was noted among those whose disease failed to heal. In general, the more severe the clinical syndrome in adults, the less likely is healing, in contrast to observations in children and in epidemics among young adults in military camps, where more than 95% heal.<sup>11, 12</sup>

Certain histologic findings in relation to the outcome of acute glomerulonephritis are shown in table 3. Among the 16 patients whose disease healed, definite glomerular hypercellularity was found in all glomeruli of 13, while two had equivocal and one had no hypercellularity. Even severe glomerular hypercellularity can be followed by healing, provided other glomerular damage does not develop. Glomerular hyalinization, crescents,

lobular necrosis or scarring was found in 13 of the 16 patients whose disease became chronic. One hundred thirty of 377 glomeruli in this group were so involved. Five of the 16 patients whose disease healed clinically had similar but generally milder and less frequent changes. In the healed group, 25 of 339 glomeruli were so involved. Red blood cell or heme casts in the tubules of those who became chronic also were more common than in those whose disease healed. As shown in table 4, diffuse interstitial fibrosis or moderately severe focal fibrosis was commonly found in the patients whose nephritis became chronic, while in general such changes were less frequent

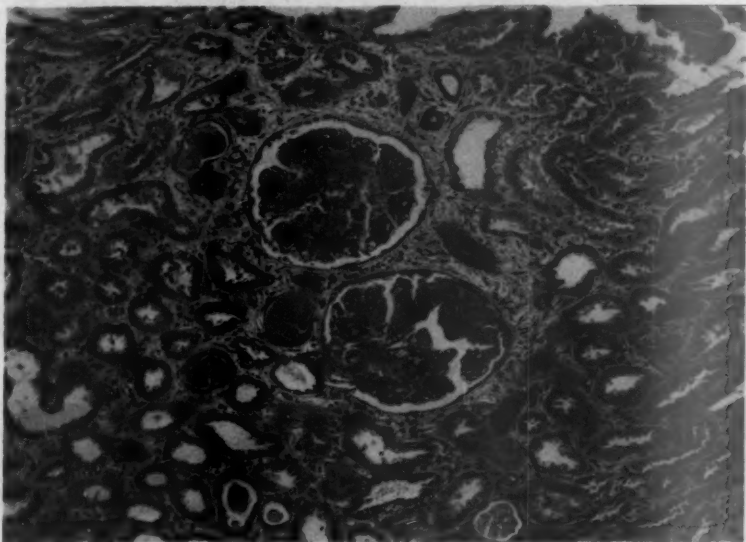


FIG. 4. Renal biopsy from patient Ape. with poststreptococcal acute glomerulonephritis, 22 days after onset. This patient's nephritis failed to heal. Both glomeruli in the figure are hypercellular. One shows an adhesion to Bowman's capsule. Much of the hypercellularity is due to intracapillary polymorphonuclear neutrophils. Considerable diffuse interstitial edema and fibrosis are present. Some of the proximal tubules are lined by a regenerative type of epithelium. Note the red cell casts in four dilated distal tubules on the left side of the figure. (Fixed in Helly's fluid, 2 $\mu$  section, 130 $\times$ , Heidenhain's connective tissue stain.)

in the healed group. Two of the three patients in the healed group who had moderate focal fibrosis were 59 and 66 years old, and also had moderately severe arteriolar disease.

All instances of acute nephritis are not associated with hemolytic streptococcal infections (table 5). Either focal or diffuse glomerulonephritis can complicate subacute bacterial endocarditis.<sup>18</sup> Acute glomerulonephritis has been described following pneumococcal pneumonia,<sup>14</sup> but the possibility of associated streptococcal infections was not rigorously excluded. In the late winter of 1956 we studied, with Richard Bates, 10 patients at Great Lakes

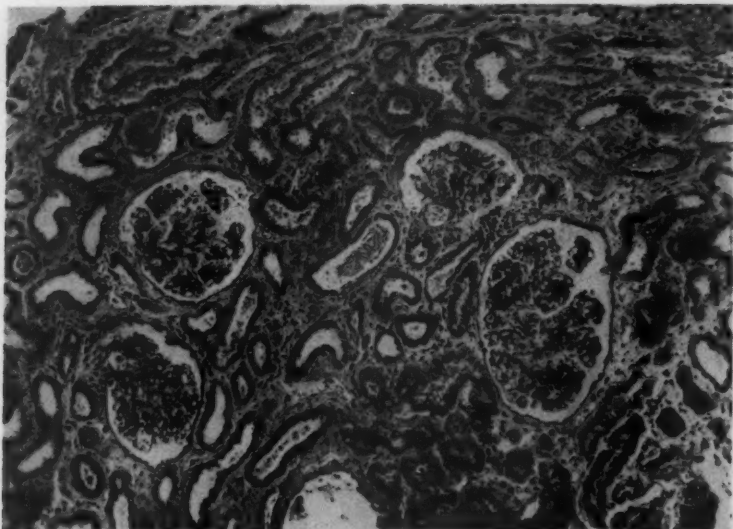


FIG. 5. Renal biopsy from patient Ape., 69 days after onset and 49 days after first biopsy. Note the prominent diffuse interstitial fibrosis; also, the glomeruli are now less hypercellular than in figure 4. Some capillary loops are widely patent, although all lobules in the proper plane of section show lobular stalk thickening and hypercellularity. (Fixed in Helly's fluid, 2 $\mu$  section, 130 X, Heidenhain's connective tissue stain.)

Naval Hospital with acute hemorrhagic nephritis in whom adequate study revealed no evidence of recent streptococcal infection.<sup>15</sup> The nephritis was mild, and prompt recovery the rule. These attacks followed pharyngitis which appeared to be viral in origin. Renal biopsies revealed focal glo-

TABLE 2  
Certain Clinical Features of Poststreptococcal Acute Glomerulonephritis

	Outcome	
	Healed	Chronic
Number of patients	16	16
Gross hematuria	8	7
Edema	6	12
Hypertension	7	13
Blood urea nitrogen > 20 mg. %	7	13
Edema, hypertension + N retention	5	10

TABLE 3  
Renal Biopsy Findings in Poststreptococcal Acute Glomerulonephritis

	Outcome	
	Healed	Chronic
Number of patients	16	16
Glomerular hypercellularity	13	16
Glomerular damage*	5	13
Red blood cell casts in tubules	4	15

\* Necrosis, lobular scars, crescent formation, adhesions or hyalinization.

TABLE 4

Interstitial Fibrosis on Renal Biopsy in Poststreptococcal Acute Glomerulonephritis

Interstitial Fibrosis	Healed	Outcome	Chronic
None	6		1
Focal—mild	7		5
Focal—moderate	3		5
Diffuse	0		5
Total	16		16

merular hemorrhage but no hypercellularity. Three similar patients were studied at Great Lakes in the winter of 1958, and one in Chicago. Other nonstreptococcal etiologies of clinical acute nephritis undoubtedly exist.

Consideration of chronic renal disease is less satisfactory, since we are rarely certain of the time of onset, etiologic clues are few, and the same histologic pattern may occur in different diseases. The subsequent analyses

TABLE 5

Etiologies of Acute Nephritis

Preceding Infection	Our Patients
Hemolytic streptococcal infection	36
Subacute bacterial endocarditis	0
Pneumococcus pneumonia	0
Great Lakes (viral ?)	14
Others	?

are limited to patients with at least one adequate renal biopsy and with adequate streptococcal antibody studies. Several characteristic patterns do emerge. In all but eight of 37 patients with chronic diffuse proliferative glomerulonephritis on biopsy, the disease followed acute nephritis of proved or probable streptococcal origin (table 6). Type 12 antibodies were demonstrated in 12 patients. We feel rather strongly that chronic diffuse proliferative glomerulonephritis is almost always the result of poststreptococcal

TABLE 6

Origin of Histologic Chronic Diffuse Proliferative Glomerulonephritis

Origin	Number of Patients	Type 12 Hemolytic Streptococcal Antibodies
Proved strep. AGN*	20	7
Probable strep. AGN†	9	4
Unknown	8	1
Total	37	12

\* Clinical acute glomerulonephritis that followed infection in which group A hemolytic streptococci were recovered on culture and/or in which significant increase in serum antistreptolysin, antistreptokinase or antihyaluronidase titer was demonstrated on serial measurements.

† Clinical acute glomerulonephritis that followed in one to four weeks an infection that, by history, could have been due to the hemolytic streptococcus but in which cultures were not obtained and in which sera for antistreptolysin titer were first obtained six months or more after infection.

acute nephritis that failed to heal, i.e., the chronic phase of Longcope's Type A<sup>3</sup> or Ellis' Type 1<sup>4</sup> nephritis.

Our experience in 109 patients with chronic proteinuria is summarized in table 7. The largest group is that just discussed: cases of chronic diffuse proliferative glomerulonephritis. Proved or presumptive evidence of streptococcal infection shortly before onset was obtained in 29 of these 37 patients. Nine of this group have developed the nephrotic syndrome. The nephrotic syndrome, however, may occur in a variety of other renal diseases, the majority of which on clinical grounds would have been classified Type B by Longcope or Type 2 by Ellis. In five patients with the nephrotic syndrome, renal biopsy revealed normal glomeruli by ordinary light microscopy. Presumably electronmicroscopy would reveal the diseased epithelial cell foot processes described by Farquhar.<sup>16</sup> Four other patients with the nephrotic syndrome had diffuse thickening of the glomerular capillary basement membranes. A similar but focal process was noted in six patients

TABLE 7  
Histologic Diagnosis on Renal Biopsy in 109 Patients with Chronic Proteinuria

Histologic Diagnosis	Number Patients	Evidence of Strep. Infection	Nephrotic Syndrome
Diffuse proliferative glomerulonephritis.	37	29	9
Epithelial cell disease	5	0	5
Diffuse membranous nephritis	4	0	4
Focal membranous nephritis	6	0	0
Focal proliferative nephritis	18	2	2
Hyaline droplets in proximal tubules	10	1	0
Interstitial fibrosis +/or vascular disease	13	1	0
Others (K-W, amyloid, etc.)	16	1	3
Total	109	34	23

with chronic but mild proteinuria, while focal proliferative changes, occasionally associated with focal membranous changes, were found in another 18 patients. Three of the latter had proved systemic lupus erythematosus, and two had diffuse arteritis. Renal biopsy in still other patients with chronic proteinuria revealed either normal kidneys except for hyaline droplets in the tubules, interstitial fibrosis, or mild arteriolar changes. Finally, in 16 patients, renal biopsy demonstrated lesions characteristic of Kimmelstiel-Wilson disease, renal vein thrombosis, amyloidosis, pyelonephritis or arteriolonephrosclerosis. These data are presented merely to emphasize the point that many patients with chronic proteinuria and other clinical evidence of chronic nephritis but with little or no evidence of associated streptococcal infection have, on histologic study, various lesions quite different from those of chronic diffuse proliferative glomerulonephritis so characteristically associated with the hemolytic streptococcus.

The concept that all forms of glomerulonephritis represent various manifestations of the same disease is untenable.

## ACKNOWLEDGMENT

We are greatly indebted to Dr. Craig W. Borden and Dr. Martin P. Hutt, of the Veterans Administration Research Hospital, to Dr. Francesco del Greco, of Passavant Memorial Hospital, and to the following members of the U. S. Naval Hospital, Great Lakes: Captain J. B. Butler, USN, Captain George M. Davis, USN, Lt. Commander Richard C. Bates, MC, USNR, Lt. Commander Alexander Minno, MC, USNR, Lt. Commander Jan K. Siemsen, MC, USNR, Lieutenant Paul W. Saltzman, MC, USNR, and Lieutenant Jonas Sode, MC, USNR, for their generous assistance, and for their permission to use data from certain of their patients.

## SUMMARY IN INTERLINGUA

Esseva facite un correlation inter le cursos clinic e serial observationes biopctic del ren in 36 patientes adulte con sporadic glomerulonephritis acute in qui le morbo sequeva un confirmate infection streptococcal hemolytic. Le acute nephritis se resolveva in 16 e deveniva chronic in 16. Un patiente moriva durante le phase acute. Esseva etiam notate quatro exacerbationes in tres patientes con glomerulonephritis chronic.

Es presentate, schematicamente, un conception possibile del historia natural de glomerulonephritis poststreptococcal. Duo casos illustrative es describe brevemente.

Circa un medietate del patientes con restablimento e un medietate del patientes con disveloppamento de chronicitate habeva hematuria grossier, sed un significative-mente plus alte incidentia de edema, de hypertension e de retention de nitrogeno esseva notate in le casos que non esseva curate. Hypercellularitate glomerular esseva constatate in quasi omne le glomerulos de ambe gruppos, sed injurias glomerular (necrosis, crescentes, adhesiones, o cicatrization) e etiam fibrosis interstitial esseva multo plus commun in le subjectos in qui le morbo deveniva chronic que in le subjectos qui se restabliva.

Non omne casos de nephritis acute es associate con infection streptococcal hemolytic. Isto es exemplificate per le occurrentia de nephritis acute in association con subacute endocarditis bacterial e pneumonia pneumococcal e per le casos de nephritis acute (de etiologia possibilemente viral) que esseva reportate ab le Hospital Naval Great Lakes in Illinois.

Inter 109 patientes con proteinuria chronic, il esseva constatate per biopsias renal que 37 habeva chronic glomerulonephritis proliferative diffuse. Omne iste 37 casos, con le exception de 8, occorreva post confirmate o probabile infectiones streptococcal hemolytic. Dece-duo del 37 habeva in lor seros anticorpore streptococcal hemolytic tipo 12. Le syndrome nephrotic complicava le nephritis in novem del 37 patientes, sed iste phenomeno occorreva etiam in le curso de altere morbos glomerular. Altere diagnoses histologic in patientes con proteinuria chronic includeva "nephrosis" (novem casos), nephritis de membrana focal (sex casos), nephritis proliferative focal (18 casos), guttetas hyalin in tubulos proximal (10 casos), fibrosis interstitial e/o morbo vascular (13 casos), e miscellane morbos renal como per exemplo morbo de Kimmelstiel-Wilson, amyloidosis, thrombosis de vena renal, e pyelonephritis (16 casos).

Le idea que omne formas de glomerulonephritis representa varie manifestationes del mesme morbo es intenibile.

## BIBLIOGRAPHY

1. Rammelkamp, C. H., Jr., and Weaver, R. S.: Acute glomerulonephritis. The significance of variations in the incidence of the disease, *J. Clin. Investigation* 32: 345, 1953.
2. Wertheim, A. R., Lyttle, J. D., Loeb, E. N., Earle, D. P., Jr., Seegal, B. C., and Seegal, D.: The association of type specific hemolytic streptococci with acute glomerulonephritis, *J. Clin. Investigation* 32: 359, 1953.

3. Longcope, W. T.: Studies on the variations in antistreptolysin titer of blood serum from patients with hemorrhagic nephritis. II. Observations on patients suffering from streptococcal infections, rheumatic fever, and acute and chronic hemorrhagic nephritis, *J. Clin. Investigation* **15**: 277, 1936.
4. Ellis, A.: Natural history of Bright's disease, *Lancet* **1**: 1, 34, 72, 1942.
5. Earle, D. P., and Seegal, D.: Natural history of glomerulonephritis, *J. Chron. Dis.* **5**: 3, 1957.
6. Earle, D. P., Jr.: Glomerulonephritis, Disease-a-Month, Jan. 1956, The Year Book Publishers, Inc., Chicago, Illinois.
7. Loeb, E. N., Lyttle, J. D., Seegal, D., and Jost, E. L.: On the permanence of recovery in acute glomerulonephritis, *J. Clin. Investigation* **17**: 623, 1938.
8. Seegal, D., Lyttle, J. D., Loeb, E. N., Jost, E. L., and Davis, G.: On the exacerbation in chronic glomerulonephritis, *J. Clin. Investigation* **19**: 569, 1940.
9. Murphy, F. D., and Schulz, E. G.: Natural history of glomerular nephritis; a report of patients treated from ten to twenty-five years after the acute stage, *Arch. Int. Med.* **98**: 783, 1956.
10. Bloom, W. L., and Seegal, D.: The nephrotic phase: its frequency of occurrence and its differential diagnostic value in determining the nature of the renal lesion in 120 patients who died of renal failure, *Ann. Int. Med.* **25**: 15, 1946.
11. Hansborg, H.: Untersuchungen über die Prognose der Scharlach Nephritis, *Acta med. Scandinav.* **61**: 570, 1924-25.
12. Stetson, C. A., Rammelkamp, C. H., Jr., Krause, R. M., Kohen, R. J., and Perry, W. D.: Epidemic acute nephritis: studies on etiology, natural history and prevention, *Medicine* **34**: 431, 1955.
13. Baehr, G., and Lande, H.: Glomerulonephritis as a complication of subacute streptococcus endocarditis, *J. A. M. A.* **75**: 789, 1920.
14. Seegal, D.: Acute glomerulonephritis following pneumococcal lobar pneumonia, *Arch. Int. Med.* **56**: 912, 1935.
15. Bates, R. C., Jennings, R. B., and Earle, D. P.: Acute nephritis unrelated to group A hemolytic streptococcus infection, *Am. J. Med.* **23**: 510, 1957.
16. Farquhar, M. G., Vernier, R. L., and Good, R. A.: An electronmicroscope study of the glomerulus in nephrosis, glomerulonephritis and lupus erythematosus, *J. Exper. Med.* **106**: 649, 1957.

## THE PATHOGENESIS OF LEPTOSPIRAL JAUNDICE\*

By F. RAMOS-MORALES, M.D., R. S. DÍAZ-RIVERA, M.D., F.A.C.P., A. A. CINTRÓN-RIVERA, M.D., JOSÉ A. RULLÁN, M.D., A. S. BENENSON, Colonel (MC),† and JOSEFINA ACOSTA-MATIENZO, M.S.,  
*San Juan, Puerto Rico*

ALTHOUGH the pathogenesis of jaundice in leptospirosis (Weil's disease) has been the subject of a great deal of speculation, it has been most frequently attributed to hemolysis and intrahepatic biliary obstruction. Many textbooks either tacitly avoid the subject or conclude, reflecting the general opinion, that the exact pathogenesis of jaundice in this disease is unknown.<sup>1</sup> The scarce material in the American medical literature does not reflect the complete clinical picture of the disease, since most of the patients studied presented intense jaundice and were severely ill.<sup>2-4</sup> Medical reports from Europe, frequently based on a large number of cases, lack laboratory observations to warrant objective conclusions on the pathogenesis of the icterus.<sup>5,6</sup> The suggestion of a coexistent duodenitis with obstruction at the ampulla of Vater<sup>7</sup> remains unconfirmed and appears to be untenable.<sup>8</sup> Intrahepatic biliary obstruction<sup>4,8</sup> has not been corroborated by either clinical or pathologic studies.<sup>7,9</sup> The significantly altered indirect van den Bergh reaction of serum bilirubin encountered in infected guinea pigs has led some investigators to postulate that jaundice results from extensive blood destruction in the presence of an edematous, functionally impaired liver,<sup>10</sup> but studies on bilirubin partition in intensely jaundiced human cases have not been confirmatory.<sup>6</sup> Hemolysis in the early phases of the disease, and subsequent severe hepatocellular disturbances, have been adduced as explanations for the phenomenon. Thus it has been postulated that early in the course of the disease there is an elevation of the indirect serum bilirubin fraction, followed by a rise in the direct fraction, and that in the severe cases hemolysis may occur, accentuating the icterus.<sup>6</sup> However, in most of the publications, conclusive evidence of hemolysis is lacking, and in the severe cases an acute hemolytic anemia is frequently taken for granted.<sup>11</sup> The data obtained from small but well studied samples would support hepatic involvement as the most important governing factor in the production of icterus.<sup>8,12</sup>

The discrepancies regarding the exact pathogenesis of leptospiiral jaun-

\* Received for publication September 12, 1958.

From the Department of Medicine, the Clinical Research Laboratory of the University of Puerto Rico School of Medicine, the San Juan City Hospital, and the Tropical Research Laboratory, U. S. Army, San Juan, Puerto Rico. This work was supported in part by Contract No. DA-49-007-MD-493, Office of the Surgeon General, Department of the Army, Washington, D. C.

† Director, Division of Immunology, Walter Reed Institute of Research, Washington, D. C.

Requests for reprints should be addressed to Francisco Ramos-Morales, M.D., Department of Medicine, School of Medicine, San Juan, Puerto Rico.

dice have prompted us to study this conspicuous aspect of the disease in view of its increasing recognition in many parts of the world.

#### MATERIAL

The analysis of the data contained in this paper was obtained from the study of 235 cases of leptospirosis in Puerto Rico from 1948 to 1956. The diagnosis was confirmed by one or more of the following criteria: (1) isolation and identification of the leptospira from blood, urine and/or spinal fluid; (2) serologic evidence of infection (complement fixation and/or agglutination-lysis tests) consistent with the clinical findings, and (3) post-mortem evidence. The clinical picture of the disease was analyzed in 208 cases and is the subject of another communication.<sup>18</sup> Of the 235 cases studied, 120 were icteric and 115 were anicteric. The hospitalization of 50% of the patients on or before the fifth day of illness gave us ample opportunity to obtain dependable information on the appearance of icterus from

TABLE 1  
Correlation of Lowest Hemoglobin and Maximal Bilirubin Values in 87 Icteric Cases  
(Minimum of Four Hemoglobin and Bilirubin Determinations at Different Stages of the Disease)

		Maximal Bilirubin in mg. %				
		2.1-9.9	10-19.4	20-29.9	30-39.9	40+
Hemoglobin values in gm. %	Below 7	1 case	1 case	2 cases	0	1 case
	7-9.9	6 cases	7 cases	1 case	5 cases	0
	10-12.9	12 cases	12 cases	11 cases	4 cases	1 case
	13-16	6 cases	13 cases	3 cases	1 case	0

early in the course of the disease, and on the mechanisms involved in its production.

*Observations on Hemoglobin and Bilirubin Values:* Eighty-seven icteric cases had four or more hemoglobin and bilirubin determinations during different stages of the disease, and at least one determination was made prior to the ninth day of illness. It must be emphasized that no specific correlation was evident between the lowest hemoglobin and the maximal bilirubin values (table 1). The intensity of the icterus was variable in cases with hemoglobin levels of or below 9.9 gm. per 100 c.c. of blood, and, generally, the lowest hemoglobin values appeared when the icterus was subsiding. Thus, no relation of cause and effect between anemia and jaundice could be established. The relation of the lowest recorded hemoglobin levels to the presence or absence of jaundice and of hemorrhagic manifestations is depicted in table 2. The icteric cases had a minimum of three hemoglobin determinations at different stages of the disease, while most of the anicteric

TABLE 2

Correlation of Lowest Hemoglobin Values with Hemorrhagic Manifestations in the Icteric and Anicteric Cases  
(Icteric cases had a minimum of three hemoglobin determinations, and the anicteric, two or more.)

Hemoglobin in gm. %	Icteric Hemorrhagic Manifestations				Anicteric Hemorrhagic Manifestations			
	Present		Absent		Present		Absent	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Below 7	4		1		0		1	
7-9.9	14	33	11	24.5	1	8	12	15
10-12.9	28		26		10	92	34	
13-16	9	67	11	75.5	2		39	85
Total	55		49		13		86	

had two or more. The hemorrhagic manifestations were either internal (subcutaneous or mucosal) or external (epistaxis and blood loss from the gastrointestinal and genitourinary tracts). Twenty-nine per cent of the icteric cases and 14% of the anicteric showed hemoglobin values of or below 9.9 gm. per 100 c.c. of blood. Among the icteric group with hemorrhagic manifestations, there were eight cases with moderate to severe gastrointestinal bleeding or epistaxis. It was observed that the lowest hemoglobin levels were recorded among those suffering from moderate to severe external blood loss. In two others, one icteric and another anicteric, there was a severe hookworm infestation. If all these cases are excluded, considering that external blood loss does not contribute to the formation of bilirubin, hemoglobin levels below 9.9 gm. were present in 22.1% of the icteric and

TABLE 3

Correlation of the Lowest Hemoglobin Values with Hemorrhagic Manifestations After Exclusion of Cases with Moderate or Severe External Blood Loss

Hemoglobin in gm. %	Icteric Hemorrhagic Manifestations				Anicteric Hemorrhagic Manifestations			
	Present		Absent		Present		Absent	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Below 7	0		1		0		1	
7-9.9	10	21	10	23	1	8	11	14
10-12.9	28		26		10	92	34	
13-16	9	79	11	77	2		39	86
Total	47		48		13		85	

13.3% of the anicteric cases (table 3). No correlation between the presence or intensity of icterus and the hemorrhagic manifestations could be ascertained.

*Observations Pertaining to Hemolysis:* The results of the tests to demonstrate hemolytic or hemorrhagic factors were unrewarding (table 4). The bleeding and clotting times and the osmotic fragility of the red blood cells were within normal limits. The direct and indirect Coombs' tests and the acid and cold hemolysins and cold agglutinin tests were negative. The capillary fragility was normal in 20 patients and increased in four, three of whom had no hemorrhagic manifestations. Serial reticulocyte counts, performed in 12 cases, revealed increased levels of 2.5 and 5% in only two instances. Single reticulocyte counts were within normal limits during different stages of the disease in 14 additional cases. The quantitative determinations of 24-hour fecal urobilinogen by Watson's method<sup>14</sup> showed daily values below 130 mg. in three anicteric cases. In one icteric patient with

TABLE 4  
Tests for Hemolytic or Hemorrhagic Tendencies in Leptospirosis

Test	Icteric			Anicteric		
	Cases	Normal	Abnormal	Cases	Normal	Abnormal
Bleeding time	17	17	0	3	3	0
Clotting time	17	17	0	3	3	0
Capillary fragility	17	14	3	7	6	1
Reticulocytosis	8	6	2	4	4	0
RBC fragility	4	4	0	2	2	0
Coombs' test	7	7	0	3	3	0
Acid hemolysins	6	6	0	2	2	0
Cold hemolysins	5	5	0	3	3	0
Cold agglutinins	4	4	0	1	1	0

anemia (case 1), the four-day average of stool urobilinogen was within normal limits, although once 521 mg. were recovered from a massive stool (table 5). There was neither hemoglobinemia nor hemoglobinuria, and no abnormal morphologic configuration of the erythrocytes suggesting increased fragility was encountered.

*Observations on Liver Function Tests:* An abnormal cephalin flocculation test of from 2 to 4 plus in 48 hours was encountered in 81% of the icteric cases. Transitory elevations of the thymol turbidity from 9 to 20 Maclagan's units were recorded in 8% of the cases. Transitory elevation of the alkaline phosphatase of up to 15.5 Bodansky units was present in 17% of the icteric. Mild to moderate reduction of the plasma prothrombin activity, with a maximum of 27 seconds (control, 15 seconds), was recorded in 13%. All of the patients with hypoprothrombinemia responded favorably to parenteral vitamin K. It must be emphasized that there was no correlation between the alterations in the prothrombin time and the hemorrhagic

TABLE 5  
Twenty-four Hour Urine and Stool Urobilinogen in One  
Icteric and Three Anicteric Cases

Day of Disease	Urobilinogen (24 hours) in mg.							
	Stool				Urine			
	Case				Case			
	I	II	III	IV	I	II	III	IV
5	None	50	42	94		2.9	0.6	1.9
6	None	15.5	34	41	30	8.7	0.12	7.1
7	None	30.2	16	73	22.6	6.8	0.04	
8	130	30.2	23		42.6	10		
9	521	None	16		120	7.4	0.07	
10	129	19			26	1.8	0.04	
11	None	47			25	0.6		
12	None	84			11	4.1		
13	None				1.5	1.0		
14	None				3.3			
15	None				1.1			
16	51				0.14			

manifestations, which renders hypoprothrombinemia an improbable cause of hemorrhage in leptospirosis. The total serum cholesterol was normal in the 22 cases tested. However, serial determinations showed low levels of cholesterol esters in five of the nine cases tested (table 6). The serum proteins were studied by the sodium sulfate fractionation method in 37 cases. Albumin values below 3 gm. per 100 c.c. were recorded in 10 cases, from 3.0 to 3.9 gm. in 17, and of 4 gm. or more in 10. Serum globulins of over 3 gm. per 100 c.c. were found in 27 of the 37 cases tested. Significant increases of serum albumin were observed during convalescence among those cases showing the lowest values early in the course of the disease.

Abnormal cephalin flocculation tests were observed in 67% and transitory elevations of thymol turbidity in 4% of the anicteric cases. In these,

TABLE 6  
Results of Hepatic Tests in Leptospirosis

	Icteric			Anicteric		
	Cases	Abnormal	Normal	Cases	Abnormal	Normal
Cephalin flocculation	64	52	12	21	14	7
Thymol turbidity	83	7	76	52	2	50
Prothrombin time	46	6	40	5	0	5
Serum cholesterol, total	22	0	22	3	0	3
Serum cholesterol esters	9	5	4	2	1	1
Serum globulins	32	22	10	12	6	6
Bromsulfalein	—	—	—	6	4	2
Alkaline phosphatase	30	5	25	2	2	2

TABLE 7  
Relation of Onset of Jaundice to Duration of the Disease in 84 Cases

Day of Onset.....	1	2	3	4	5	6	7	8	9	10	13	14	16
Cases	3	7	10	21	14	8	13	2	2	1	1	1	1

the alkaline phosphatase, prothrombin time and total serum cholesterol were within normal limits. The cholesterol esters were abnormal in one instance. The bromsulfalein test was abnormal in four of the six anicteric cases tested, with maximal values of 36% retention in 45 minutes (table 6). The serum albumin varied from less than 3 gm. per 100 c.c. in two cases, to 3.0 to 3.9 gm. in four, and to 4 gm. or over in five.

*Observations on Bilirubin and Urobilinogen:* Jaundice of variable intensity was present in approximately 50% of the cases. This appeared by the fifth day of illness in 65%, and by the seventh in 90% of the cases

TABLE 8  
Interval from Appearance of Jaundice and Maximal Bilirubin Values in 66 Cases  
Admitted Before the Eighth Day of Illness

Interval in Days....	1	2	3	4	5	6	7	8	9	12
Cases	8	5	6	9	12	9	7	8	1	1

(table 7). The highest values of serum bilirubin were observed within the first seven days after the onset of jaundice in 85% of the cases (table 8). In some instances the interval from the onset of icterus to the highest values of serum bilirubin was judged to be shorter than that recorded because the highest bilirubin values were present on admission. Jaundice persisted for an average of 32 days, with ranges of from one to 70 days. There was no pruritus, and the urine was generally positive for bile. Slight to moderate hepatomegaly was encountered in 70% of the cases. This finding was as frequent in the icteric as in the anicteric group. Light-colored stools were transitorily observed in four of the icteric cases.

TABLE 9  
Values of Urinary Urobilinogen in Leptospirosis by Different Methods

I. Dilution	Over 1:20	Below 1:20
Icteric	12	26
Anicteric	17	22
II. Ehrlich units (2 hrs.)	Over 1	Below 1
Icteric	16	2
Anicteric	8	2
III. Quantitative (Watson's method)	High	Normal
Icteric	1	—
Anicteric	2	1

Concomitant elevations of the one-minute fraction were observed whenever the 30-minute serum bilirubin exceeded 3.0 mg. per 100 c.c. An analysis of the daily serum bilirubin partition in 12 patients who had 30-minute values ranging from 1.5 to 3 mg., and who subsequently developed intense jaundice, shows that the one-minute fraction ranged from 25 to 75% (average, 50%). In four cases where the maximal daily 30-minute bilirubin ranged from 1.6 to 2.3 mg., the one-minute fraction constituted 18 to 25% of the total. In two other cases the maximal 30-minute bilirubin fractions were 1.6 and 1.9 mg., with one-minute fractions of 37.5 and 42%, respectively. A transitory retention type of bilirubinemia, with values from 1.6 to 3.3 mg. in 30 minutes, and one-minute fractions of 19 to 33%, was observed during the convalescence of six icteric cases. These alterations had no correlation with the hemorrhagic manifestations.

The urobilinogen determinations in 109 cases (57 icteric and 52 anicteric) are summarized in table 9. Urobilinogen was determined by the urine dilution method in 77 cases, but these results are considered to be of limited clinical value because of the methods employed. In some cases the urine was not examined immediately after collection; 14 patients with normal values were receiving chlortetracycline; the majority of the icteric patients had intense yellowish orange coloration of the urine, even after the precipitation of the bilirubin with calcium salts, which interfered with the reading of the pink color, and, on occasions, a green or brown color appeared on adding the Ehrlich's reagent. Twenty-four of 28 cases tested had an increased two-hour urinary urobilinogen. This was as frequent in the icteric as in the anicteric. The average of the highest value in the icteric cases was 5.4 Ehrlich units, and in the anicteric, 4.2 units, with maximal values of 9 units in each group. Determinations by the dilution method had shown normal values in several of these cases. The 24-hour urinary urobilinogen determinations by Watson's method<sup>14</sup> were significantly abnormal in one icteric and in two of the three anicteric cases tested. However, the highest values were recorded in the icteric case.

#### CASE REPORTS

*Case 1.* A 46 year old mechanic experienced the sudden onset of frontal headaches, chills, fever, nausea, vomiting, dull right upper abdominal pain, generalized body aches and pains, and scanty, reddish urine. Jaundice appeared two days after onset. On the fourth day he was acutely ill and had a sunburned appearance. Temperature, 100° F.; pulse, 84; respirations, 18; blood pressure, 110/80 mm. of Hg. The bulbar and palpebral conjunctivae were markedly injected, and the sclerae were yellow. A slit lamp examination showed an aqueous flare in the fluid of the anterior chamber of the eye. The heart and lungs appeared to be normal, the pharynx was injected, and the liver was tender and could be palpated 2 cm. below the right costal margin. The patient showed exquisite generalized muscular tenderness.

The hemoglobin values varied from 8 to 10 gm. per 100 c.c., and the total serum bilirubin was 6.0 mg. on the eighth day. The urinary urobilinogen showed a maximal value of 120 mg. (table 10). The red cells appeared to be normal in size and shape,

and there was reticulocytosis of 2.6% on the twelfth day of illness. The urine showed a trace of protein, and the nonprotein nitrogen was 35 mg. per 100 c.c. The cephalin flocculation test was negative; thymol turbidity, 2 units; alkaline phosphatase, 6.9 Bodansky units. Coombs' test, the acid and cold hemolysin and the cold hemagglutinin tests, and the serologic test for syphilis, were negative. There were no ova or parasites in the stools. A positive complement fixation test for leptospirosis developed in the second week of illness.

The patient received daily intravenous injections of 1,500 c.c. of 5% glucose in physiologic saline solution during the febrile period, with adequate urinary output. There were daily spikes of fever up to 101° F. until the tenth day of illness, when most of the toxic symptoms disappeared, and jaundice subsided within the first two weeks after onset. The patient was discharged as well on the sixteenth day after admission.

TABLE 10  
Hemoglobin, Serum Bilirubin and Urobilinogen Determinations in Case 1.  
(Note the Retention Type of Bilirubinemia (thirteenth day))

Day of Disease	Hemoglobin (gm./100 c.c.)	Serum Bilirubin (mg./100 c.c.)		Urobilinogen (mg./24 hrs.)	
		1 Min.	30 Min.	Urine	Stool
6				30.1	—
7	10			22.6	—
8	9.8	3.1	6.0	42.6	129
9	10.5			120	521
10				26.2	129
11				24.5	—
12				10.8	—
13	8.0	0.48	1.7	1.5	—
14				3.3	—
15	9.2			1.1	—
16				0.14	41
18				0.6	14.4

*Comment:* This case presents some features suggestive of a hemolytic process. Although the low hemoglobin values might have existed prior to the onset of illness, the appearance of mild reticulocytosis on the twelfth day suggests that the anemia may have appeared during the course of the disease. The increased stool urobilinogen on the ninth day depreciates in significance when the four-day average is considered. The low percentage of the one-minute bilirubin fraction on the thirteenth day may well be ascribed to hepatic dysfunction, demonstrated by the increased urinary urobilinogen. This is unique among the 235 cases of leptospirosis studied, since it was the only one showing features suggestive of a hemolytic process. Whether a hemolytic process coexisted with the accompanying evidence of hepatic dysfunction remains unanswered, since red blood cell survival tests were lacking.

*Case 2.* A 23 year old Puerto Rican male suddenly developed chills, high fever and severely painful right inguinal lymphadenopathy, requiring bed-rest. On the third day of illness he appeared to be acutely ill and extremely toxic, with a temperature of 105° F., pulse of 120, respirations of 24 per minute, and a blood pressure

of 120/80 mm. of Hg. He had severe bulbar and palpebral conjunctivitis, a non-tender liver felt 1 cm. below the right costal margin, moderately enlarged and tender inguinal lymph nodes, muscular tenderness and questionable rigidity of the neck muscles. He had leukocyte counts of 6,600 to 14,000, with 70 to 85% neutrophils, hemoglobin values of 6.5 to 14 gm. per 100 c.c., and red cell counts of 2,200,000 to 4,700,000 per cubic millimeter of blood. The total serum bilirubin reached levels of 48 mg. per 100 c.c. on the twelfth day of illness. The cephalin flocculation test was 3 plus in 48 hours, but the thymol turbidity test was normal. The prothrombin time was increased to 27 seconds (control, 15 seconds), but was readily corrected with parenteral vitamin K. The nonprotein nitrogen was 159 mg. per 100 c.c. on the eighth day of illness (figure 1). The platelet counts varied from 102,000 to 188,000 per cubic millimeter of blood. There was moderate proteinuria. Ova of *Necator americanus* were found in the stools. The spinal fluid was found negative. The capillary fragility was normal. Serologic tests for syphilis, brucella, typhus and infectious mononucleosis were negative. Repeated blood cultures were negative.

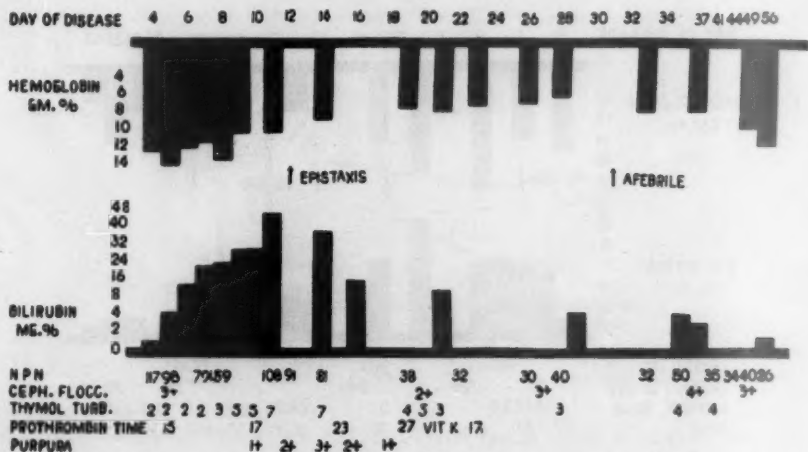


FIG. 1. Case 2. Depicting hemoglobin, bilirubin and other values in icteric leptospirosis.

for bacterial pathogens, and blood smears were negative for microfilariae. *Leptospira icterohemorrhagiae* were repeatedly isolated from the blood and spinal fluid from the fourth to the tenth day of illness. A significantly positive complement fixation test for leptospirosis appeared on the seventh day of illness.

The inguinal adenopathy subsided on the fifth day, when the patient developed jaundice. Vomiting and persistent hiccup appeared on the sixth day, and the urinary output, which had been under 1,000 c.c. per day, increased to 2,400 c.c. on the seventh day. On the tenth day of illness a soft, tender liver was palpated 5 cm. below the right costal margin, and petechiae appeared, mainly over the chest. On the twelfth day of illness the patient became drowsy, vomited constantly, complained of severe headache, and developed multiple ecchymoses and moderately severe epistaxis. By the fourteenth day the vomiting subsided and he was lucid. During the next six days the purpura and hepatomegaly subsided, and by the twenty-eighth day he was afebrile. The jaundice gradually decreased, and he was discharged as well 50 days after admission.

*Comment:* This is a severe case of icteric leptospirosis where the high levels of serum bilirubin cannot be explained by a hemolytic process. The intense jaundice preceded the onset of the anemia, which may well have been explained on the basis of blood loss due to severe epistaxis and purpura. It must be emphasized that retrospective estimates revealed that around 1,000 c.c. of blood were used for various laboratory tests, including cultures of the leptospirases.

*Case 3.* A 38 year old Puerto Rican male was hospitalized 19 days after a rat urinated on his face. Two weeks after this disagreeable experience he suddenly developed diffuse abdominal pain, chills, high fever, severe nausea and vomiting, frontal headache, general malaise, and muscular aches and pains. On the fifth day of illness he appeared to be acutely ill and dehydrated, and presented a sunburned complexion. Temperature, 101° F.; pulse, 98; respirations, 20 per minute; blood pressure, 115/72 mm. of Hg. The patient had a few hemorrhagic macules on the

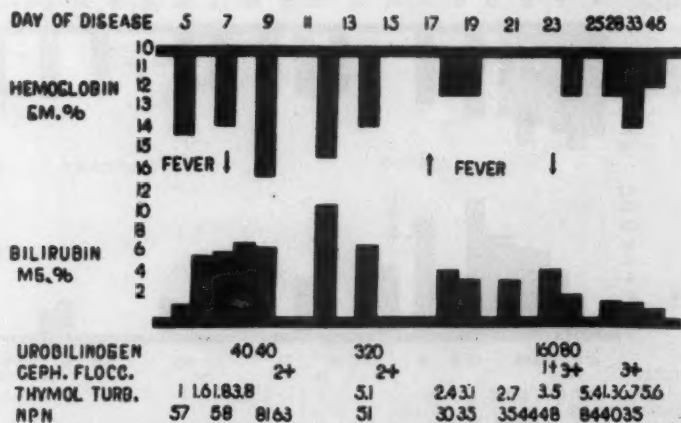


FIG. 2. Case 3. Summarizing the various laboratory results in icteric leptospirosis.

anterior chest and right forearm, severe bulbar and palpebral conjunctivitis, injection of the ear drums, soft palate and pharynx, a barely palpable, nontender liver, and moderate muscular tenderness. No signs of meningeal irritation were elicited.

The laboratory examinations revealed: hemoglobin, 11.5 to 16 gm. per 100 c.c.; erythrocyte counts, 3,470,000 to 4,500,000 per cubic millimeter; cephalin flocculation, 3 plus; turbidity tests, normal; nonprotein nitrogen, 84 mg. per 100 c.c. There were increases in urinary urobilinogen and serum bilirubin (figure 2). The patient had a leukocyte count of 10,150, with 84 neutrophils and 16 lymphocytes, and a platelet count of 212,000 per cubic millimeter of blood. The bleeding and clotting times and the capillary fragility were within normal limits. The prothrombin time and serum alkaline phosphatase were normal. The serum albumin was 3.76 gm. and globulins, 3.30 gm. per 100 c.c. Repeated urinalyses showed mild proteinuria, pyuria and cylindruria. The spinal fluid, blood sugar and chlorides, the serum amylase and the serologic test for syphilis were negative. The chest x-rays and the electrocardiograms were within normal limits. *L. icterohemorrhagiae* were cultured from the blood and spinal fluid on the sixth, seventh and eighth days of illness, and the com-

plement fixation test for leptospirosis was significantly positive on the sixth day of illness.

Jaundice appeared on the sixth day of illness, with persistent vomiting, headache and general malaise. The temperature was normal by the eighth day, when the headache and muscle tenderness subsided. The liver was enlarged (2 cm.) and tender by the ninth day. The patient showed definite improvement when the vomiting subsided on the tenth day. However, on the seventeenth day he had a relapse of chills, fever, general malaise, headache, nausea and vomiting, with a leukocytosis of 26,200 (78% neutrophils and 22% lymphocytes). By the twenty-fifth day he was afebrile, and all toxic manifestations had disappeared. The convalescence was uneventful. The patient received supportive therapy, with bed-rest and intravenous fluids, and the urinary output was always adequate.

*Comment:* This is a case of leptospirosis with a secondary rise in temperature, moderate jaundice, no anemia, and lack of inverse relation of bilirubin and hemoglobin values during the period of increasing icterus. Increased urinary urobilinogen, high serum globulins and abnormal cephalin

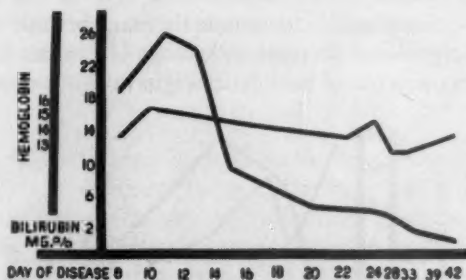


FIG. 3. Case 4. Depicting the relationship of hemoglobin and bilirubin values in a deeply jaundiced case of leptospirosis. There was no anemia.

flocculation are indicative of hepatic dysfunction. The changes of hemoglobin values may have resulted from alterations in body hydration, variations inherent in the methods for colorimetric determinations, and the multiple phlebotomies intended for numerous laboratory studies.

*Case 4.* A 19 year old Puerto Rican laborer suddenly developed chills, high fever, generalized malaise, severe muscular pains and headache. Jaundice appeared on the fourth day, with a corresponding increase in pigmentation of the urine. On the seventh day of illness he was acutely ill and deeply jaundiced, with a temperature of 103° F., pulse of 110, respirations of 24 per minute, and a blood pressure of 110/80 mm. of Hg. The conjunctivae and pharynx were injected and the sclerae deeply jaundiced. Neither the liver nor the spleen was palpable. Exquisite muscular tenderness was elicited in the extremities and back. Five years prior to the present illness the patient had been repeatedly exposed to streams contaminated with *Schistosoma mansoni*.

The laboratory examinations revealed: hemoglobin, 13 to 16.5 gm. per 100 c.c.; red cell counts, 3,650,000 to 4,350,000 per cubic millimeter; maximal values of bilirubin, 16.9 mg. in one minute and 26.8 mg. in 30 minutes (figure 3). The initial leukocyte count was 9,850 per cubic millimeter, with 78% neutrophils and 22%

lymphocytes, with further variations of from 8,900 to 10,700, with 30 to 36% mature eosinophils. The stools were positive for ova of *Necator americanus*, *Trichuris trichiura* and *Ascaris lumbricoides*. The rectal biopsy disclosed many viable *S. mansoni* eggs. There were mild and transitory proteinuria, pyuria and cylindruria. The nonprotein nitrogen varied from 31 to 48.6 mg., and the urea nitrogen from 15 to 23.3 mg. per 100 c.c. of blood. The thymol turbidity test showed 1.3 to 3.8 units, and the cephalin flocculation was not significantly altered until the twenty-eighth day of illness. The prothrombin time varied from 17 to 22 seconds. The serum albumin was 4.02 gm., and the globulins, 3.62 gm. per 100 c.c. of blood. Serial blood cholesterol determinations, started on the fourteenth day of illness, ranged from 200 to 292 mg. per 100 c.c., with 51 to 63% esterification. The two-hour urine urobilinogen determinations from the ninth to the eighteenth day of illness ranged from 0.9 to 3.1 Ehrlich units. The complement fixation for leptospirosis was strongly positive by the eighth day.

The fever, muscular pains and headache subsided on the tenth day, with gradual disappearance of the jaundice. The patient was discharged as well 46 days after admission. He received adequate treatment for the parasitoses two months after discharge.

*Comment:* It seems plausible to assume that the presence of deep jaundice in the absence of significant decrease in hemoglobin values is a clear indication that the icterus was not of hemolytic origin in this instance.

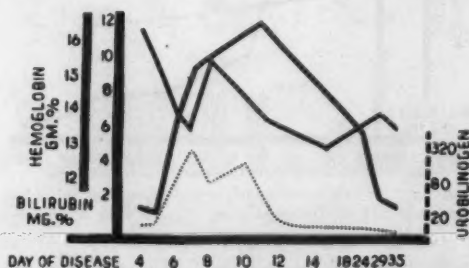


FIG. 4. Case 5. Depicting hemoglobin, bilirubin and urinary urobilinogen.

*Case 5.* A 32 year old Puerto Rican laborer experienced the sudden onset of severe muscular pains, followed by chilliness, high fever, headache, pleuritic pain, dry cough, sore throat, persistent vomiting, and watery, nonbloody diarrhea. On the fourth day of illness he appeared to be acutely ill and markedly dehydrated, with a temperature of 103° F., pulse of 110, respirations of 22 per minute, and a blood pressure of 110/70 mm. of Hg. There were mild injection of the right ear drum, intense bulbar and palpebral conjunctivitis, and marked pharyngeal injection. There were expiratory rhonchi over the left lung field, a soft, tender liver and spleen palpated 1 cm. below the costal margins, and generalized, exquisite muscular tenderness.

Repeated laboratory examinations showed: leukocyte counts, 6,550 to 7,300; hemoglobin values, 13.0 to 16.5 gm.; erythrocyte counts, 3,700,000 to 5,850,000 per cubic millimeter; maximal serum bilirubin values, 7.9 mg. per 100 c.c. in one minute, and 11.6 mg. in 30 minutes, and increased urinary urobilinogen in dilutions of 1 to 320 (figure 4). The platelet counts ranged from 66,000 to 188,000 per cubic millimeter of blood, and the bleeding, clotting and prothrombin times, capillary fragility and the serologic test for syphilis were normal. The cephalin flocculation was repeatedly abnormal; the thymol turbidity ranged from 3 to 15.5 units; the alkaline

phosphatase was normal, and the total serum proteins were 6.31 gm. per 100 c.c., with 2.5 gm. of albumin and 3.81 gm. of globulin. The nonprotein nitrogen varied from 30 to 48 mg., the blood urea nitrogen from 17 to 28 mg. per 100 c.c., and there was moderate proteinuria. The chest x-rays revealed bilateral parenchymatous infiltrations, indicative of bronchopneumonia. *L. icterohemorrhagiae* were isolated from the blood from the fifth to the eighth day of illness. The complement fixation test for leptospirosis was doubtful on the eighth but strongly positive by the eleventh day of illness.

The patient was seriously ill, with fever of 104° F., while receiving daily intravenous infusions of 1,500 c.c. of 5% glucose in normal saline solution. Jaundice appeared on the seventh day of illness. Procaine penicillin, in daily intramuscular doses of 1,200,000 units, was administered for eight days. The patient was afebrile and asymptomatic by the eleventh day. The liver was within normal limits by the seventeenth day, and he was anicteric by the thirty-fifth. There was no indication that penicillin had altered the course of the disease.

*Comment:* This case illustrates a direct correlation between the course of serum bilirubin and urinary urobilinogen levels, indicating inability of the liver to handle these pigments adequately. The high initial hemoglobin levels were perhaps best explained by the severe dehydration early in the course of the disease.

#### COMMENTS

In an acute febrile disease such as leptospirosis, the following militate against hemolysis as a dominant factor in the genesis of icterus: the absence of a consistent anemia; the failure to demonstrate the time relation of cause and effect of low hemoglobin values and jaundice among the anemic; the absence of a consistent, significant reticulocytosis, even during convalescence; the absence of hemoglobinemia and hemoglobinuria; the frequent increases in the one-minute serum bilirubin fraction; the early appearance of bile in the urine; the normal fecal urobilinogen values, and the absence of hemolytic factors.

Although anemia and reticulocytosis are not specific indications of hemolysis, these phenomena are expected to occur in an acute, severe hemolytic crisis that would lead to jaundice even in the presence of a previously undamaged liver. The occasional preferential elevation of the 30-minute serum bilirubin fraction may not be an absolute indication of hemolysis, since it has been demonstrated in hepatocellular alterations of various origin.<sup>18</sup> A mild, predominant form of indirect hyperbilirubinemia, similar to that occasionally seen during the recovery stage of viral hepatitis, was at times observed during convalescence from leptospirosis, perhaps suggesting a delay in the recovery of hepatocellular function. The increases in the late-reacting bilirubin may be also attributed to reabsorption of the tissue hemorrhages so commonly observed in the disease, since this may serve to overload the excretory capacities of the regenerating liver.

The main objection to a decreased hepatocellular function as the main governing factor of jaundice in leptospirosis has been the absence of striking morphologic changes of the liver. However, it must be emphasized that

postmortem studies frequently reveal hepatic enlargement, necrosis, cloudy swelling, blurred cellular margins, variations in the number and size of the nuclei, pyknosis, mitotic figures, fatty infiltration, enlargement of Kupffer's cells, inspissated bile in the canaliculi, dissociation of the liver cords, and focal areas of inflammation.<sup>5, 7, 8, 9, 16</sup> An analysis of reports on the postmortem findings by different authors would lead us to surmise that the liver is not normal in leptospirosis. The specificity and magnitude of morphologic hepatic abnormalities are not clearly ascertained, and it must be emphasized that the extent of the histologic alterations is not comparable to those of yellow fever or acute yellow atrophy.<sup>17</sup>

Clinical observations on the interval of the appearance of jaundice and the highest serum bilirubin levels would indicate that the most intense hepatic dysfunction appears from the seventh to the twelfth day of illness. As renal failure is the main cause of death, most of the postmortem studies are performed after the twelfth day of illness. It seems plausible to assume that by this time hepatic recovery may have been initiated. Besides, aberrations of hepatic function may occur in morphologically normal cells. This is best exemplified by the congenital hepatic dysfunction in Gilbert's disease,<sup>18</sup> and by the transitory jaundice induced by the administration of icterogenin (a South African poison), unaccompanied by hemolysis or histologic alterations of the liver parenchyma.<sup>19</sup>

Inasmuch as there is no single test to measure with accuracy the diverse functional capacities of the liver, a justification of the wide variation of the results obtained in our studies is evident. Thus, the nonspecific cephalin flocculation test, intended to reflect hepatic damage, was abnormal in 78% of our cases, and it was as frequently positive in the icteric as in the anicteric cases. The high fever and other extrahepatic factors may have altered cephalin flocculation in our cases.<sup>20</sup> On the other hand, this phenomenon may have been a reflection of liver damage in our patients. This impression may well be substantiated by the demonstration of variable degrees of jaundice and of other abnormal liver function tests.

The thymol turbidity test was abnormal in a minority of cases. The results from the cephalin flocculation and thymol turbidity tests do not always run parallel, a common experience in other liver diseases.<sup>21</sup> The production of prothrombin was occasionally and only slightly disturbed. This seems to depend upon extrahepatic factors, since it was readily corrected with parenteral vitamin K. Although total serum cholesterol values were within normal limits, the ratio of esterification was frequently reduced. This was more evident with serial determinations initiated early in the course of the disease. The return of cholesterol esterification to normal after the second week of illness demonstrates the rapid improvement in hepatic function in the icteric cases. The alterations in the serum albumin and globulins may be considered to indicate impaired liver function. This may be substantiated by the increases in serum albumin during convalescence.

The transitory elevations of alkaline phosphatase (9 to 15.5 Bodansky units) recorded in 17% of the icteric cases may have reflected an ephemeral impedance of bile flow through the biliary system, possibly intrahepatic. This may be further substantiated by the presence of light-colored stools in four cases suggesting biliary obstruction. An impairment in the passage of biliary pigments through the hepatic cellular barrier and a decreased hepatic secretory pressure might have precluded the delivery of bile to the intestines. If the mild elevations in the alkaline phosphatase and the light-colored stools were indications of intrahepatic biliary obstruction, it is logical to assume that this is not the basic cause of jaundice, but rather an aggravating factor in some of the icteric cases of leptospirosis.

It would be reasonable to believe that the presence of bile in the urine and the results of the serum bilirubin partition values are compatible with the icterus of hepatocellular insufficiency. The rare instances of the retention type of bilirubinemia early and/or during convalescence of the disease do not militate against hepatocellular jaundice.<sup>15</sup> The inability of the hepatic cells properly to dispose of the urobilinogen load absorbed from the gastrointestinal tract, manifested by an increase of urinary urobilinogen, serves as strong evidence in support of a deficient hepatic function. However, it must be clarified that the reliability of urinary urobilinogen determination depends upon the accuracy of the methods employed, as some of these may frequently lead to false-negative results. It seems to us as if the normal values recorded in the 14 patients receiving chlortetracycline may well be explained by a decreased urobilinogen production in the intestinal tract.<sup>22</sup> Since the excretion of urobilinogen is generally decreased in renal disease with azotemia,<sup>23</sup> false-negative results are not rare in the most severe forms of leptospirosis.<sup>10</sup> Furthermore, the two-hour urinary urobilinogen test may yield 15% of false-negative results in cases with significantly increased urobilinogenuria.<sup>24</sup> However, the data obtained from the two-hour and the 24-hour determinations demonstrate a significant increase in urinary urobilinogen in both the icteric and the anicteric cases. The diminished brom-sulfalein excretion would also indicate a decreased hepatic functional capacity in the anicteric cases. Though the presence of fever might have led to abnormal retention,<sup>25</sup> our data would suggest other alterations as the main governing factors.

There is enough evidence to suggest that the absorption of tissue hemorrhages contributes to increasing bilirubin loads, but this does not appear to be the main cause of jaundice in leptospirosis. If the tissue hemorrhages were extensive enough to be the sole cause of jaundice, a significant degree of anemia should be expected in the severely icteric cases. There is enough clinical proof to suggest that there is no correlation between red cell and hemoglobin values and the hemorrhagic manifestations, if those cases with moderate or severe external blood loss are excluded. It can be ascertained that deep jaundice with normal hemoglobin and red cell values in many

icteric cases militates against tissue hemorrhages as an important pathogenetic factor of jaundice.

It must be emphasized that about 10% of the serum bilirubin is derived from iron porphyrins not comprising the hemoglobin molecule.<sup>26</sup> The extensive muscle lesions in leptospirosis have been previously described.<sup>27</sup> However, an increased myoglobin catabolism has not been determined, and neither myoglobinemia nor myoglobinuria has been observed in human leptospirosis. Even with extensive myoglobin destruction in man, the jaundice would remain unexplained in the absence of hepatic dysfunction.<sup>28</sup>

The low hemoglobin values, more frequent among the icteric than among the anicteric, are not conclusive evidence of hemolysis. It seems to us as though the anemia in leptospirosis is best explained by a combination of additive factors, such as external blood loss, tissue hemorrhages, decreased caloric intake, and a negative nitrogen balance in a febrile disease with azotemia. Probably some of the cases had decreased hemoglobin levels prior to the onset of the disease, which is a not unusual finding in our environment. In retrospect, and quite unsuspected, the amount of blood used for repeated and duplicated laboratory analyses, as well as for isolation of leptospira and serologic tests, was estimated as 250 to 1,000 c.c. per patient, and the greater amounts were obtained from the icteric cases. The role of the phlebotomies in the development of anemia cannot be definitely ascertained. Besides, 15 patients had hookworm infestations, which undoubtedly contributed to the low red cell and hemoglobin levels.<sup>29</sup>

#### SUMMARY

An analysis of the data obtained from the study of 235 cases of leptospirosis would indicate that there is no evidence in support of hemolysis as a dominant factor in the genesis of icterus. No relation of cause and effect of anemia and jaundice was evident. Severe bilirubinemia appeared with unaltered red cell or hemoglobin values in the well hydrated patients. Even among the anicteric, anemia may be attributed to blood loss, either internal or external, a negative nitrogen balance, high fever, azotemia (most prominent among the icteric, but rather common among the anicteric), parasitic infestations with chronic blood loss, and, in some instances, frequent phlebotomies for numerous laboratory examinations.

Laboratory evidence of hepatic dysfunction was recorded in both the anicteric and the icteric: abnormal cephalin flocculation, hyperbilirubinemia, urobilinogenuria, abnormal bromsulfalein test, and impairment in synthesis of the serum proteins and cholesterol esters. The most intense hepatic dysfunction occurred during the second week of illness, as evidenced by the maximal increases in bilirubin and the alterations in cholesterol esterification.

It must be emphasized that there are generally increases of the one- and of the 30-minute serum bilirubin. A predominant 30-minute hyperbilirubinemia is occasionally observed early in the course of the disease and during convalescence. This phenomenon may be governed by either a de-

creased hepatic functional capacity or increasing loads of pigment derived from the reabsorption of tissue hemorrhages. It appears that the latter is of secondary importance in the pathogenesis of the jaundice in leptospirosis. Transitory biliary tract obstruction, possibly intrahepatic, may be an aggravating factor in a minority of the icteric cases. The role of the impaired renal function in the maintenance of hyperbilirubinemia remains a subject for inquiry.

Since there is no evidence to suggest that an increased catabolism of iron porphyrins (myoglobin) contributes to the development of jaundice, it is apparent that the most important governing factor in the pathogenesis of icterus in leptospirosis is a decreased functional capacity of the liver.

#### SUMMARY IN INTERLINGUA

Un studio de 235 casos de leptospirosis pare indicar que il existe nulle supporto pro le these que hemolyse intravascular es un factor dominante in le genese de ictero. Esseva notate nulle correlation inter le presentia de anemia e de ictero. Sever grados de ictero esseva observate in ben-hydratate patientes con normal valores hemoglobinic e erythrocytic. Le anemia de leptospirosis pote esser attribuite a un combination de factores, incluse perditas externe de sanguine, histohemorrhagias, negativitate del balancia de nitrogeno, azotemia, coexistentia de infection parasitic, e—in alcun casos—frequente phlebotomias effectuate pro numerose studios laboratorial.

Indicios laboratorial de dysfunction hepatic esseva trovate in casos icteric e anicteric. Istos includeva anormalitate del flocculation cephalinic, hyperbilirubinemia, urobilinogenuria, defectos del synthese de proteinas e de esteris cholesterolic in le sero, e un retention anormal de bromsulfaleina. Le dysfunction hepatic esseva le plus marcate durante le secunde septimana del morbo.

Le fractiones de bilirubina seral de un minuta e de 30 minutas es generalmente augmentate. In certe casos, un predominante fraction de bilirubina indirecte es observate durante le phases precoce del morbo e durante le convalescentia del patiente. Le reabsorption de histohemorrhagias e transiente obstructions biliari intra le hepate es possiblemente factores aggravante, in le disveloppamento de ictero in un minoritate del casos. Le plus importante factor dominante in le pathogenese de ictero in leptospirosis pare esser le reduce capacitate functional del hepate.

#### BIBLIOGRAPHY

1. (a) Harrison, T. R.: Principles of internal medicine, 1954, The Blakiston Co., New York.  
(b) Strong, R. P.: Stitt's diagnosis, prevention and treatment of tropical diseases, 1944, The Blakiston Co., Philadelphia.
2. Bertucci, E. A., Jr.: Leptospirosis, *Am. J. M. Sc.* 209: 86, 1945.
3. Ashe, W. F., Pratt-Thomas, H. R., and Kumpe, C. W.: Weil's disease, *Medicine* 20: 145, 1941.
4. Senekjic, H. A.: The clinical manifestations of leptospirosis in Louisiana, *J. A. M. A.* 126: 5, 1944.
5. Van Thiel, P. H.: The leptospirosis, 1948, Universitaire pers Leiden, Leiden.
6. (a) Walch-Sorgdrager, B.: Leptospirosis, *Bull. Health Organ., League of Nations* 8: 143, 1939.  
(b) Broom, J. C., and Alston, J. M.: Weil's disease: analysis of 195 cases in England, *Lancet* 2: 96, 1948.
7. Dawson, B., and Hume, W. E.: Jaundice, *Quart. J. Med.* 10: 90, 1947.

8. Kaneko, R.: Über die pathologische Anatomie der Spirochetosis icterohemorrhagica, *Schweiz. med. Wchnschr.* **65**: 531, 1935.
9. Koppisch, E., and Bond, W. M.: The morbid anatomy of human leptospirosis: a report of thirteen fatal cases, Symposium on the Leptospiroses, Medical Science Publications No. 1, U. S. Government Printing Office, 1953.
10. Busch, H.: Über die Ursache des Ikterus bei der experimentellen Weilschen Krankheit, *Beitr. z. path. Anat. u. z. allg. Path.* **96**: 233, 1936.
11. Lester, B. S., Denison, G. A., Posey, L. C., and Tate, M. G.: Weil's disease, *South. M. J.* **35**: 325, 1942.
12. Sterling, K.: Hepatic function in Weil's disease, *Gastroenterology* **15**: 52, 1950.
13. Díaz-Rivera, R. S., Hall, H. E., Ramos-Morales, F., Swisher, K. Y., de Jesús, J. A., and Benenson, A. S.: Leptospirosis in Puerto Rico. II. Clinical aspects of human infection, in press.
14. Watson, C. J., and Bilden, E.: Determination of urobilinogen in feces and in urine, *Arch. Int. Med.* **68**: 740, 1941.
15. (a) Watson, C. J.: The importance of the fractional bilirubin determination in clinical medicine, *Ann. Int. Med.* **45**: 351, 1956.  
(b) Schiff, L.: Differential diagnosis of jaundice, 1946, The Year Book Publishers, Inc., Chicago, Illinois.  
(c) Reichman, S., and Davis, W. D.: The recognition and differential features of indirect reacting hyperbilirubinemia, *Ann. Int. Med.* **46**: 523, 1957.
16. Jeghers, H. J., Houghton, J. D., and Foley, J. A.: Weil's disease, *Arch. Path.* **20**: 447, 1935.
17. Harris, W. H.: Comparison of pathologic observations in Weil's disease and in yellow fever, *Arch. path.* **34**: 663, 1942.
18. Dameshek, W., and Singer, K.: Familial non-hemolytic jaundice, *Arch. Int. Med.* **67**: 259, 1941.
19. With, T. K.: Note on pathogenesis of jaundice, *Acta med. Scandinav.* **152**: 239, 1955.
20. Moore, D. B., Pierson, P. S., Hanger, F. M., and Moore, D. H.: Mechanism of the positive cephalin cholesterol flocculation reaction in hepatitis, *J. Clin. Investigation* **24**: 292, 1945.
21. Watson, C. J., and Rappaport, E. M.: A comparison of the results of the Hanger cephalin cholesterol flocculation test and the MacLagan thymol turbidity test in patients with liver disease, *J. Lab. and Clin. Med.* **30**: 983, 1945.
22. Sborov, V. M., Jay, A. R., and Watson, C. J.: The effect of Aureomycin on urobilinogen formation and the fecal flora, *J. Lab. and Clin. Med.* **34**: 1743, 1949.
23. (a) Royer, M., and Solari, A. V.: Depuración plasmática de la urobilina, *Rev. Soc. argent. de biol.* **17**: 329, 1941.  
(b) Watson, C. J.: The bile pigments, *New England J. Med.* **227**: 665, 1942.  
(c) Watson, C. J.: The bile pigments, *New England J. Med.* **227**: 705, 1942.
24. Voegtlin, W. L., Moss, H. M., and March, E.: A comparison of the quantitative urinary urobilinogen determination (Watson) with the urine Ehrlich test, *Gastroenterology* **14**: 583, 1950.
25. Hicks, M. H., Holt, W. P., Guerrant, J. L., and Leavell, B. S.: The effect of artificially induced fever on liver function, *J. Clin. Investigation* **27**: 580, 1948.
26. (a) London, I. M., West, R., Shemin, D., and Rittenberg, D.: On the origin of bile pigment in normal man, *J. Biol. Chem.* **184**: 351, 1950.  
(b) London, I. M., West, R., Shemin, D., and Rittenberg, D.: On the origin of bile pigment in normal man, *J. Biol. Chem.* **184**: 373, 1950.
27. Sheldon, W. R.: Lesions of muscle in spirochetal jaundice, *Arch. Int. Med.* **75**: 119, 1945.
28. Wintrobe, M. M.: Clinical hematology, 1956, Lea and Febiger, Philadelphia.
29. Wells, R. S.: Observation on the blood sucking activities of the hookworm, *A. caninum*, *J. Parasitol.* **17**: 167, 1931.

## A CRITICAL ANALYSIS OF THE USE OF SALICYLAZOSULFAPYRIDINE IN CHRONIC ULCERATIVE COLITIS \*

By CHARLES G. MOERTEL, M.D., and J. ARNOLD BARGEN, M.D., F.A.C.P.,  
*Rochester, Minnesota*

OF the many disease states that the internist or general practitioner may be called upon to treat, few if any have proved to be more frustrating to the physician and more demoralizing to the patient than chronic ulcerative colitis. Evaluation of any form of therapy in this disease is a most complex task, since it occurs in varied clinical forms and in varied degrees of severity. In many cases the natural history is one of exacerbations and remissions. Therefore, any therapeutic agent, if given at an opportune time or for a sufficiently long period, may be coincident with an unrelated amelioration of symptoms. Physiologically active medications may produce side-effects that partially overshadow the symptoms of the disease and thereby distort comparison with untreated controls. It was with full recognition of these limitations that the present study, an evaluation of the effectiveness of salicylazosulfapyridine (Azulfidine) therapy, was undertaken.

### PHARMACOLOGY OF SALICYLAZOSULFAPYRIDINE

This drug, under the more common names Azulfidine, Azopyrine and Salazopyrine, was devised and produced through the combined efforts of Dr. Nanna Svartz and the A. B. Pharmacia of Stockholm. Svartz<sup>1</sup> first reported it in 1941 as a promising therapeutic agent for chronic ulcerative colitis. It was later introduced into the United States by one of us, who reported favorable results with it in 1948.<sup>2</sup>

The molecular structure of salicylazosulfapyridine is, in essence, a combination of salicylic acid and sulfapyridine, these two substances being linked by a diazo bond (figure 1).

When this substance is taken orally, it is partially absorbed and partially excreted with the feces (figure 2). We have been unable to demonstrate any antibacterial effect of this medication on the stool flora. A portion of the absorbed drug is excreted unchanged in the urine. The remainder

\* Received for publication May 12, 1959.

Presented at the Fortieth Annual Session of The American College of Physicians, Chicago, Illinois, April 20, 1959.

From the Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Requests for reprints should be addressed to the Section of Publications, Mayo Clinic, Rochester, Minnesota.

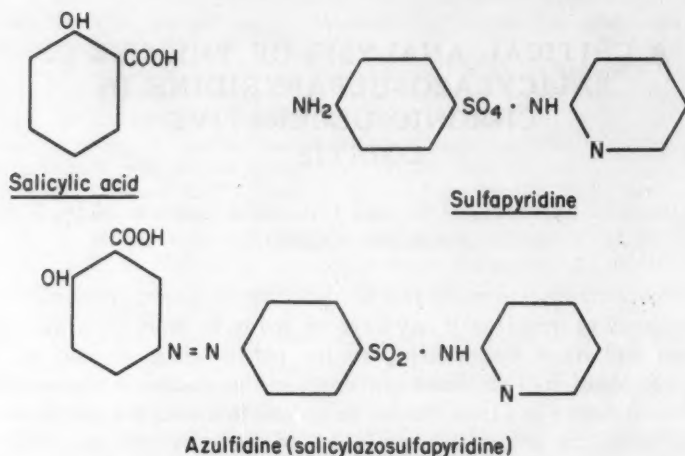


FIG. 1. Molecular structure of salicylazosulfapyridine.

is apparently stored in collagen and elastic tissue, the affinity for these tissues being thought to result from the acid azo structure of the drug.<sup>3</sup> According to Svartz,<sup>4</sup> it is during the period of storage in the collagen tissues that the therapeutic action of salicylazosulfapyridine takes place, but the mechanism of this therapeutic effect is obscure. In the connective-tissue stores the drug is apparently broken down, with the gradual release of aminosalicic acid and sulfapyridine into the blood. With the average daily dose of the drug, the blood levels of salicylate and of sulfapyridine are both considerably lower than would be expected in therapeutically active treatment with either salicylates or sulfapyridine alone.

Salicylazosulfapyridine is generally given in doses of 6 to 8 gm. a day. In refractory patients it can be given, and usually is tolerated, in doses as high as 16 gm. a day. A satisfactory therapeutic effect can frequently be obtained with a daily dose of 4 gm. in patients who are intolerant to larger

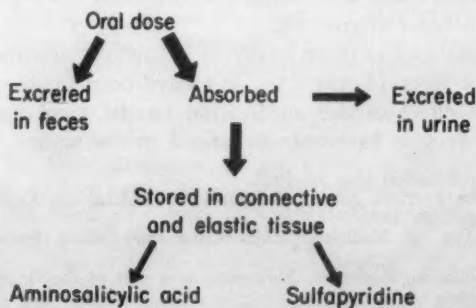


FIG. 2. Disposition of salicylazosulfapyridine by the body.

amounts. For maintenance therapy, it has proved satisfactory to give the drug in two-week courses separated by a one-week rest period.

Side-effects of treatment, consisting chiefly of nausea, vomiting or headache, are observed in approximately 15% of patients. In the majority the side-effects are transitory and subside spontaneously, or can be circumvented by temporarily discontinuing use of the drug and then gradually building the dose to therapeutic levels. Allergic reactions are less common than the aforementioned symptoms, and consist chiefly of skin rashes, febrile reactions and arthralgias. Occasionally these can be adequately controlled by antihistamines, but they usually require discontinuing use of the drug. Serious complications of therapy are rare and are entirely hematologic. Two cases of severe agranulocytosis have been observed at the Mayo Clinic, and three have been reported in the literature.<sup>4-6</sup> This complication has produced the single fatality reported as attributable either directly or indirectly to salicylazosulfapyridine therapy. An additional, less serious hematologic change that may be observed is anemia. This was first reported by Svartz,<sup>4</sup> and recently Spriggs and associates<sup>7</sup> have defined this as a Heinz-body anemia of the type that previously was reported in sulfapyridine and sulfanilamide therapy. This change has never been observed to reach severe proportions in patients treated with salicylazosulfapyridine, and can be reversed by discontinuing use of the drug.

#### PURPOSE OF PRESENT STUDY

The purposes of the present study were (1) to evaluate the symptomatic response to salicylazosulfapyridine therapy as compared with the symptomatic response in similar groups of patients treated with other sulfonamide preparations and treated with general measures alone, and (2) to compare in a general way the results of salicylazosulfapyridine treatment with those of long-term ACTH or steroid therapy.

#### MATERIAL AND METHOD

Patients included in the study were those seen for the first time at the Mayo Clinic in the period January 1, 1948, through December 31, 1952, with the diagnosis of chronic ulcerative colitis confirmed by proctoscopic or roentgenologic examination of the colon, or by both procedures. Patients included were only those who had been observed and treated in the hospital for 10 or more consecutive days.

Because of the early limited supply of salicylazosulfapyridine, and because of the personal preferences of the individual consulting physicians, the patients treated during this period were divided into three major groups:

1. Those treated with salicylazosulfapyridine (183 patients).
2. Those treated with sulfonamide drugs other than salicylazosulfapyridine (109 patients: 71 treated with Sulfathalidine, 25 with azo-

sulfamide [Neoprontosil], six with sulfacetamide, four with phthalyl sulfacetamide [Thalamyd], and three with Sulfasuxidine).

3. Those treated with general measures alone, or general measures supplemented with antibiotics (131 patients).

Patients were included in groups 1 or 2 only if they had been treated with salicylazosulfapyridine or other sulfonamides for a minimum of seven days. Also, in order not to weight the study in favor of salicylazosulfapyridine or sulfonamides, patients who were unable to take medications by mouth because of intestinal perforation, impending perforation or extreme toxicity were not included in the study. All patients in each of the three groups were treated with the usual general and supportive measures, including partial or complete rest in bed, a bland, low residue, high protein, high caloric diet, supplemental vitamins and blood transfusions when needed, as well as with sedatives, narcotics, antispasmodics, and specific antibiotics when indicated.

TABLE 1  
Severity of Symptoms by Treatment Group

Group	Percentage of Patients According to Severity of Symptoms			
	Mild	Moderate	Moderately Severe	Severe
1. Salicylazosulfapyridine	3	19	61	17
2. Other sulfonamides	2	25	58	15
3. General measures	7	20	61	12

The patients in each of the three groups were then separated into four categories according to the severity of presenting symptoms, as follows:

Mild: Patient had (1) mild diarrhea, (2) minimal or no rectal bleeding, (3) minimal or no loss of weight, and (4) no fever.

Moderate: Patient had two or more of the following symptoms: (1) five to 10 rectal discharges a day, (2) persistent gross blood in the stools or mild anemia (hemoglobin, 10 to 11.5 gm. per 100 c.c. of blood), and (3) loss of 5 to 10% of the usual body weight.

Moderately severe: Patient had two or more of the following symptoms: (1) 10 to 15 rectal discharges a day, (2) moderately severe rectal bleeding or moderately severe anemia (hemoglobin, 8.5 to 10 gm.), (3) daily temperature of 100 to 102° F., and (4) loss of 10 to 20% of the usual body weight.

Severe: Patient had two or more of the following symptoms: (1) more than 15 rectal discharges a day, (2) severe rectal bleeding or severe anemia (hemoglobin, less than 8.5 gm.), (3) daily temperature of more than 102° F., and (4) loss of more than 20% of the usual body weight.

As is shown in table 1, there was no significant difference between the three treatment groups in regard to clinical severity of the disease presented by the constituent patients. Other factors, such as duration of symptoms, complications of the disease, and extent and severity of colonic involvement, were likewise closely comparable.

The response to treatment in each of the three groups was judged only by the following objective criteria: (1) reduction in frequency of rectal discharges, (2) reduction of fever, (3) reduction in rectal bleeding, and (4) regaining of lost weight. Subjective impressions of improvement expressed by the consulting physician were not considered in the evaluation. Observations recorded over the last four days of hospitalization were used as the basis for grading each patient's response to treatment, as follows:

Condition worse: Self-explanatory.

Condition unimproved: Self-explanatory.

Condition improved: All of the following criteria were met: (1) reduction of rectal discharges to less than one-half of the frequency on admission, (2) gross blood in the stools minimal or absent, (3) no fever, and (4) weight stable or increasing.

Clinical remission: All of the following criteria were met: (1) average of three or fewer stools a day, (2) no rectal bleeding, (3) no fever, and (4) recovery of five or more pounds of weight lost.

## RESULTS

The over-all results of treatment, graded according to the criteria listed above, are presented in figure 3. It can be seen that the proportion of patients showing a favorable response to sulfonamides other than salicylazosulfapyridine is little different from the proportion showing a favorable response to general measures alone. The small advantage of 46% over 39% could quite possibly be explained by the longer average hospitalization accorded the sulfonamide-treated group. The favorable response attained by 64% of the patients treated with salicylazosulfapyridine during essentially the same average period of hospitalization would seem to represent a definite therapeutic advantage attributable to this medication. This same advantage in clinical response was observed in all degrees of clinical severity of the disease (figure 4). It should be emphasized that these results represent only the response of the patients while they were in the hospital, where their progress could be closely observed and documented. Many patients who showed only stabilization or slight improvement in the hospital showed more definite improvement or a symptomatic remission as they continued on their treatment program at home.

The comparative effect of salicylazosulfapyridine therapy on frequency of rectal discharges, fever and gain or loss of weight is presented in figure 5. The changes observed in these manifestations of chronic ulcerative colitis

are objective in nature, can be numerically recorded, and are therefore less vulnerable to the distortions that personal prejudice or enthusiasm may produce. In each of these clinical manifestations, salicylazosulfapyridine therapy is shown to produce more favorable results when compared with those attained with other sulfonamide preparations and with general measures alone.

The duration of the disease was not found to influence the effectiveness of salicylazosulfapyridine therapy materially. Also, the drug was found to be as effective in patients with inflammatory complications, such as arthritis or erythema nodosum, as it was in patients with uncomplicated disease. Typical forms of the disease as well as atypical enterocolitis and segmental forms seemed to respond favorably to treatment with this

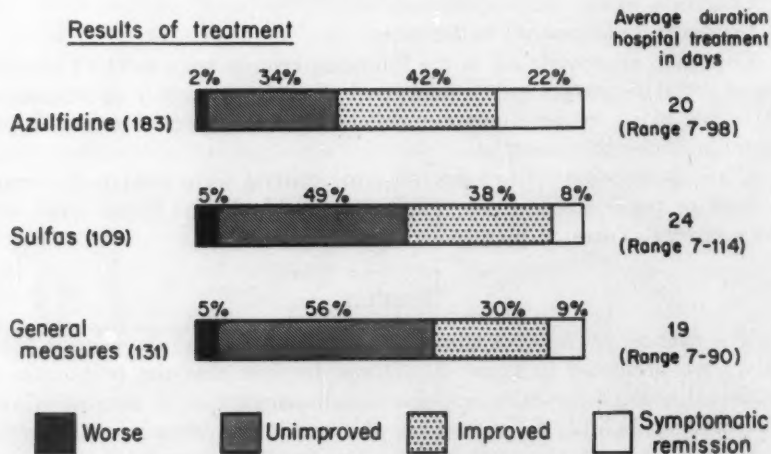


FIG. 3. Over-all results of treatment.

drug. It must be stated, however, that salicylazosulfapyridine is far from a panacea for chronic ulcerative colitis. Some patients show no response to treatment with it, and more show only partial clinical recovery. Nevertheless, our observations would seem to indicate that it is a very effective agent in the symptomatic control of the disease. The results reported here represent our earliest experiences with this medication. Further refinements in the technic of its administration have seemed to produce even more favorable results. When treatment with salicylazosulfapyridine is added to the basic program of management of chronic ulcerative colitis, a good response is observed in a greater percentage of patients than we have observed with any other mode of therapy.

To be recommended for general use in the treatment of chronic ulcerative colitis, salicylazosulfapyridine must also produce an over-all more favor-

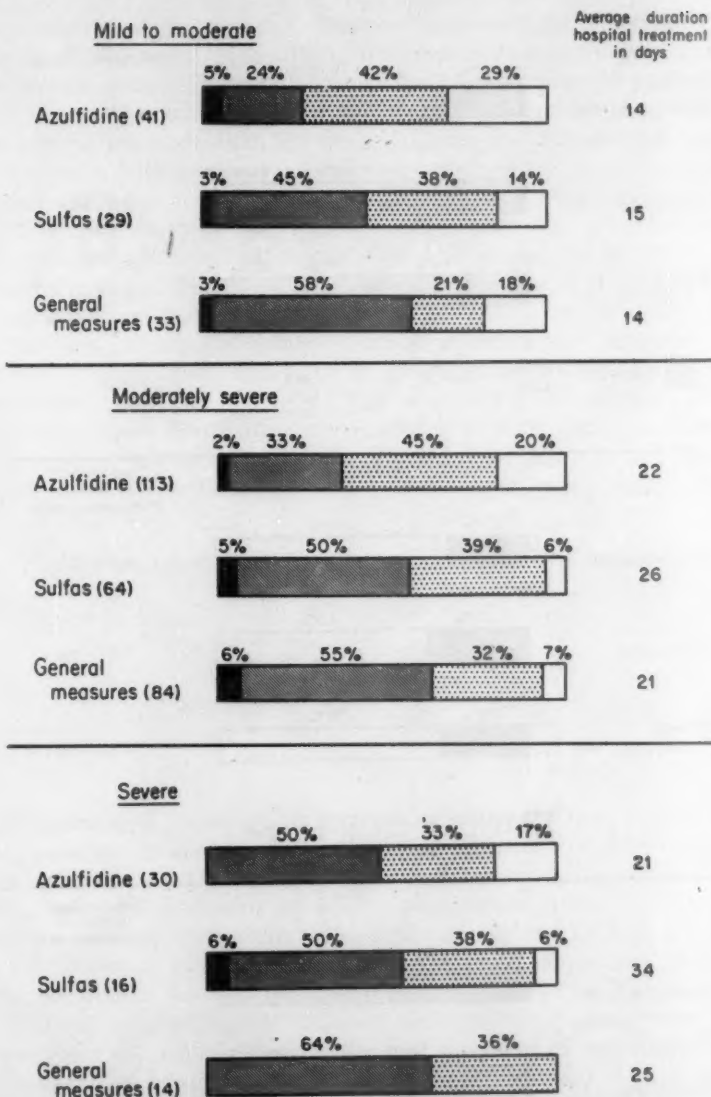


FIG. 4. Results of treatment according to clinical severity of disease.

able result than that obtained with the other currently favored method of therapy, the long-term use of large doses of ACTH and steroids. Fierst and associates<sup>8</sup> observed that the incidence of improvement in their patients treated with salicylazosulfapyridine was comparable with the incidence in

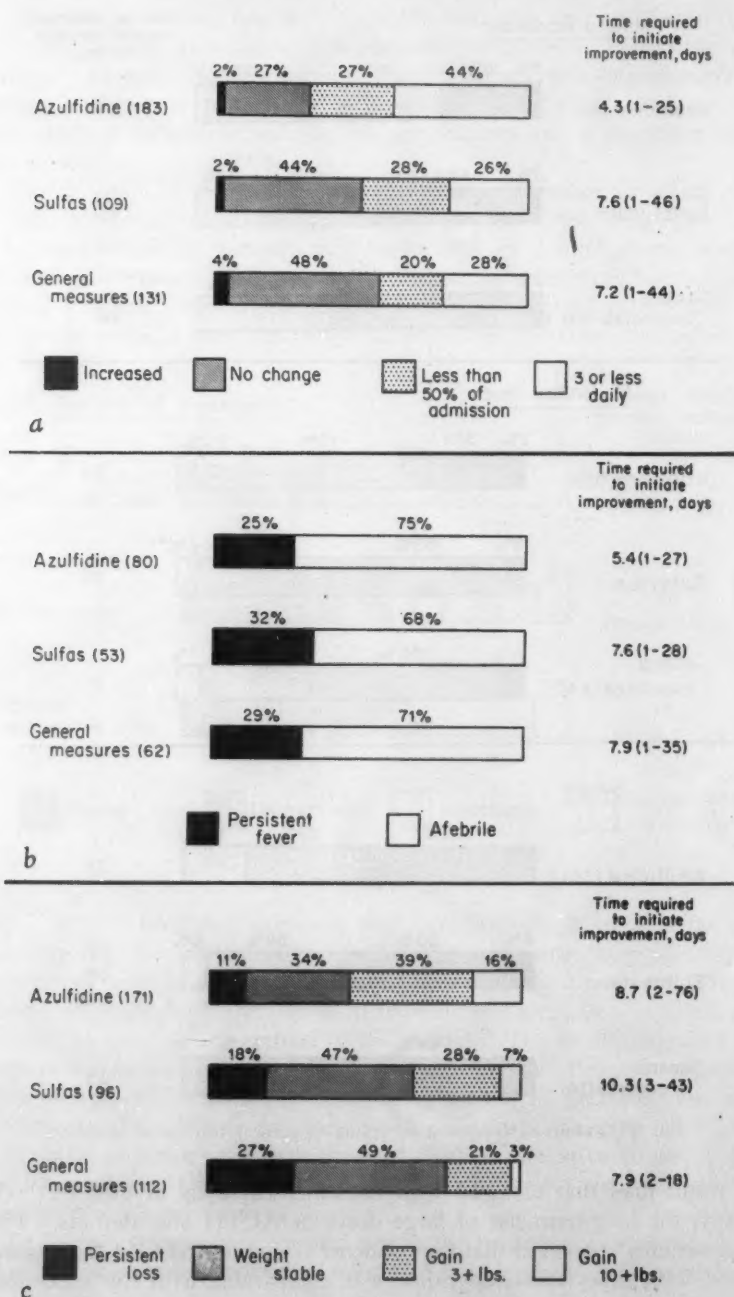


FIG. 5. Effect of treatment on (a) frequency of rectal discharges, (b) fever, and (c) recovery of weight lost.

those treated with steroids. Their salicylazosulfapyridine-treated group was small, however. It is difficult to compare with any degree of validity the results obtained in our study with the results reported by others using ACTH or steroids, since there undoubtedly is considerable variation in the criteria for evaluating severity of disease and response to treatment. It does seem both necessary and appropriate, however, to compare the two methods of treatment in general terms.

The large majority of patients in this study who were treated with salicylazosulfapyridine had disease that had proved to be more or less intractable to previous therapy. Eighty-five per cent of them had had one or more previous hospitalizations, and 24% had had treatment with ACTH or cortisone but reported either no improvement or only temporary amelioration of symptoms. For many, colectomy and ileostomy had been recommended elsewhere. In this group of patients with difficult problems, 64% experienced substantial improvement or a symptomatic remission after an average of less than three weeks of hospital therapy with salicylazosulfapyridine. With continued treatment at home or on an outpatient basis,

TABLE 2  
Side-Effects of Salicylazosulfapyridine Therapy in 183 Patients

Side-Effect	Patients
Nausea	15
Nausea and vomiting	9
Nausea and headache	2
Headache	2
Nausea, headache and fever	1
Fever	1
Dermatitis	1
Total	31(17%)

this incidence of improvement increased to 78%. These results are not unique in our hands alone, since a similar incidence of improvement has been reported in each of the three other large series in which this drug was employed. Improvement was reported by Morrison<sup>9</sup> in 70% of 60 patients, by Lagercrantz<sup>10</sup> in 79% of 82 patients, and by Svartz<sup>11</sup> in 77% of 403 patients. This incidence of improvement is comparable to the most favorable results reported for long-term therapy with ACTH or steroids.

Patients responding to treatment with salicylazosulfapyridine usually show noticeable improvement in the first few days of treatment, and can be managed on an ambulatory basis after only a relatively short hospitalization. The average hospitalization period of three weeks for the 183 patients in this series compares favorably with the average period of from six to eight weeks required in a roughly comparable group of 180 patients treated with large doses of ACTH or steroids by Kirsner and associates.<sup>12</sup>

The complications of treatment to which a patient may be subjected are also an important factor in the evaluation of a program of therapy. The complications encountered during salicylazosulfapyridine therapy by the

patients in this study are listed in table 2. No serious complications occurred in any of the 183 patients, and only 6% had persistent side-effects that necessitated discontinuing use of the drug. All of the other side-effects were minor and transitory. When the incidence of these is compared with the incidence of serious complications incurred in even the most experienced hands with long-term therapy with steroids, it would seem again that salicylazosulfapyridine should be the preferred agent of treatment.

Also to be considered is the problem of discontinuing use of the medication when maximal therapeutic benefit has been obtained, or when complications of treatment become intolerable. The use of salicylazosulfapyridine may be discontinued abruptly without incident. The problem of withdrawing the patient from large doses of ACTH or steroids may be one of considerable magnitude, however.

The relapse and recurrence rate for patients in this study during the first year after their treatment with salicylazosulfapyridine was initiated is presented in table 3. Svartz<sup>11</sup> also reported that one third of her patients who responded to treatment with this drug had recurrence of symptoms; but it was her experience, as it has been ours, that many of these are again

TABLE 3  
Status During the First Year Following Initiation of Therapy in Patients  
Whose Condition Improved With Salicylazosulfapyridine Therapy

Status	Per Cent of Entire Group	Per Cent of Traced Patients
Improvement persisted	57	68
Recurrence or relapse	27	32
Patients untraced	16	—

responsive to further therapy with the drug. Here again, this agent would seem to have a more favorable effect than ACTH or steroids, since most experiences reported with the corticoids have indicated a higher rate of recurrence and relapse.

#### SUMMARY AND CONCLUSIONS

Salicylazosulfapyridine has proved to be an effective agent in the control of the symptoms of chronic ulcerative colitis. When compared to treatment with other sulfonamide preparations and with general measures alone, treatment with this drug has seemed to be superior, both in respect to overall symptomatic response to therapy and in respect to duration of hospitalization required to produce a favorable response. Undesirable side-effects of treatment occur in about one of six patients treated, but these are, in the main, minor and transitory. Serious hematologic complications are rare, but blood counts should nevertheless be made periodically during therapy.

Although the initial response to long-term treatment with large doses of ACTH or steroids would seem to be comparable to the response obtained with salicylazosulfapyridine, a comparison of length of hospitalization re-

quired, complications incurred, the problem of withdrawal, and rate of recurrence or relapse seems to show that the last-mentioned drug has a very definite advantage.

Salicylazosulfapyridine is not the final answer to the treatment of chronic ulcerative colitis, but it has been shown to be of considerable usefulness in controlling the symptoms of this disease. Comparison with other commonly employed methods of therapy would seem to indicate that at present, when combined with the basic general and supportive measures, it represents the treatment of choice for chronic ulcerative colitis.

#### SUMMARIO IN INTERLINGUA

Es reportate le resultados del uso de salicylazosulfapyridina (Azulfidina) in le tractamento de 183 patientes con chronic colitis ulcerative. Quando le uso de iste droga esseva addite al programma fundamental del therapia, un favorable responsa clinic esseva notate in un plus alte procentage del patientes que quando simile gruppos de patientes habeva essite tractate con altere preparatos sulfonamidic o exclusive-mente con mesuras supportative general. In 78% del patientes tractate con salicylazosulfapyridina, appreciable grados de melioration o remission clinic esseva notate. Adverse effectos lateral esseva observate in 17%, sed in le majoritate del casos ille effectos esseva minor o transitori.

Esseva interprendite un comparison general inter le resultados total obtenite in le tractamento con salicylazosulfapyridina e le resultados del tractamento a longe vista con ACTH o steroides. Ben que le responsa initial evocate per le tractamento con ACTH o con steroides pare esser comparabile con illo evocate per salicylazosulfapyridina, le comparison del duo modos de therapia ab le puncto de vista del duration del hospitalisation requirite, del complicationes incurrite in le curso del tractamento, e del frequentia de recidivas o recurrentias pareva monstrar que salicylazosulfapyridina es definitemente preferibile.

#### BIBLIOGRAPHY

1. Svartz, N.: Ett nytt sulfonamidpreparat, *Nord. med.* 9: 554, 1941.
2. Bargen, J. A.: Evaluation of the newer therapy of ulcerative colitis, *South. M. J.* 41: 646, 1948.
3. Helander, S.: On the concentrations of some sulfanilamide derivatives in different organs and tissue structures, *Acta physiol. Suppl.* 29: 5, 1945.
4. Svartz, N.: Salazopyrin, a new sulfanilamide preparation, *Acta med. Scandinav.* 110: 577, 1942.
5. Levy, C. W. D.: Agranulocytose ved salazopyrinbruk meddelelse om et tilfelle, *Tidsskr. f. d. norske lægefor.* 69: 255, 1949.
6. Evans, R. S., and Ford, W. P., Jr.: Studies of the bone marrow in immunological granulocytopenia: following administration of salicylazosulfapyridine, *Arch. Int. Med.* 101: 244, 1958.
7. Spriggs, A. I., Smith, R. S., Griffith, H., and Truelove, S. C.: Heinz-body anaemia due to salicylazosulphapyridine, *Lancet* 1: 1039, 1958.
8. Fierst, S. M., Robinson, E., Langsam, A., Werner, A., and Ingegnb, A. P.: Corticosteroid therapy in chronic ulcerative colitis, *J. A. M. A.* 163: 1444, 1957.
9. Morrison, L. M.: Response of ulcerative colitis to therapy with salicylazosulfapyridine, *J. A. M. A.* 151: 366, 1953.
10. Lagercrantz, R.: Ulcerative colitis in children, *Acta paediat. Suppl.* 75: 89, 1949.
11. Svartz, N.: The treatment of ulcerative colitis, *Gastroenterologia* 86: 683, 1956.
12. Kirsner, J. B.: Personal communication to the authors.

## SOME UNUSUAL SYNDROMES ASSOCIATED WITH NEOPLASTIC DISEASE\*

By G. LENNARD GOLD, M.D., and BRUCE I. SHNIDER, M.D.,  
Washington, D. C.

It is usual for patients with malignant neoplasms to present with symptoms and signs produced by the anatomic location of their tumor or its metastases. Occasionally, as is the case with functioning endocrine tumors, the products of the neoplastic growths are responsible for many of the manifestations.

More recently, several abnormalities of body metabolism have been recognized in some people afflicted with neoplastic growths. Cerebellar degeneration and various neurologic syndromes have been reported in association with malignant tumors, despite the fact that no metastatic deposits could be found. Cushing's syndrome, mineralocorticoid abnormalities, hypoglycemia, hypercalcemia and polycythemia have been recorded in the presence of so-called nonfunctioning tumors of the lung, ovary, thymus, kidney and mesenchymal tissues. This report is concerned with the occurrence of four of these syndromes that we have observed in association with malignant tumors.

### CASE REPORTS

#### *I. Adrenal Functional Abnormalities:*

*Case 1.* A 48 year old white male was admitted to the National Institutes of Health for chemotherapy of a proved bronchogenic carcinoma. Six months prior to admission he had developed cough and chest pain, and these symptoms continued until two weeks prior to admission, at which time he was admitted to another hospital, where a right exploratory thoracotomy was performed. An inoperable carcinoma with pleural metastases was found. His postoperative course was uneventful. His appetite was fair, and the caloric intake varied between 800 and 1,000 calories of a hospital diet. There was no vomiting or diarrhea, nor were any mercurial diuretics or sulfonamides administered. On admission the patient appeared to be acutely ill. His vital signs were within normal limits. The important findings were a recent right thoracotomy scar, signs of weight loss, an enlarged liver and 4 plus edema of the lower extremities.

Admission blood chemical tests showed: blood urea nitrogen, 10 mg.%; fasting blood sugar, 117 mg.%; sodium, 132 mEq./L.; potassium, 2.0 mEq./L.; alkaline phosphatase, 5.2 Bodansky units; albumin, 2.1 gm.%; globulin, 3.5 gm.%. At this

\* Received for publication June 1, 1959.

Presented at the Fortieth Annual Session of The American College of Physicians, Chicago, Illinois, April 22, 1959.

From the Department of Medicine, Georgetown University School of Medicine, and the Cancer Chemotherapy Research Program, Georgetown University Medical Division, District of Columbia General Hospital, Washington, D. C.

Requests for reprints should be addressed to Bruce I. Shnider, M.D., District of Columbia General Hospital, Washington 3, D. C.

time the urine pH was 7.5, and an electrocardiogram was consistent with hypokalemia. The patient improved slowly with potassium replacement therapy, and his serum electrolytes returned to more normal values (figure 1). At this time his blood corticoids were markedly elevated (70.8 gamma%; normal range, 1 to 25 gamma%).

Urinary potassium determinations revealed no excessive loss. Aldosterone assay was within normal limits; urinary 17-ketosteroids were 17 and 23 mg./24 hours; hydroxycorticoids were 10 and 15 mg./24 hours (normal ranges 10 to 15 mg./24 hours, and 1 to 10 mg./24 hours, respectively).

The improvement noted was only temporary. After the hypokalemia was corrected, the patient's course was highlighted by several bouts of atrial flutter, controlled with digitalis and quinidine, and several episodes of dyspnea and syncope. He died suddenly on the seventeenth hospital day.

### CARCINOMA OF LUNG & HYPOCHLOREMIC ALKALOSIS

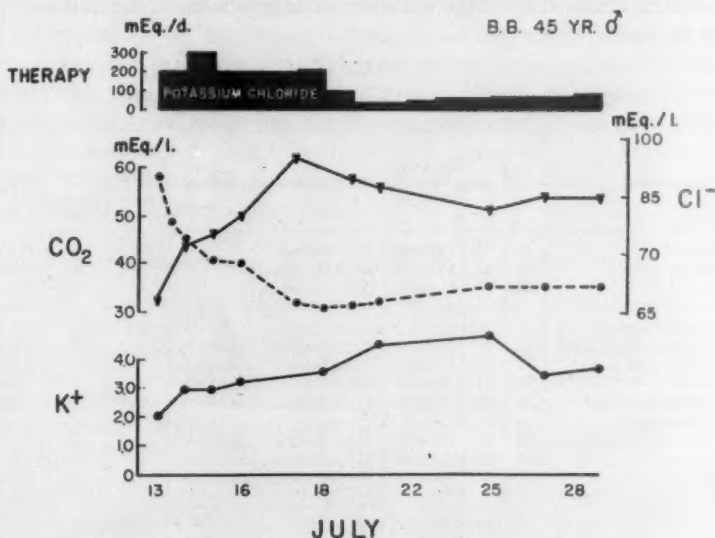


FIG. 1. Case 1. Serial determinations of serum chloride, potassium and carbon dioxide following the administration of potassium chloride.

Autopsy revealed an anaplastic carcinoma with metastatic deposits in the lungs, regional lymph nodes, skull, thyroid, parathyroid glands, adrenals and kidneys. The metastatic disease in the adrenal glands was in the zona reticularis; the zona glomerulosa appeared to be normal.

*Comment:* We believe that this patient represents a case of probable mineralocorticoid abnormality in association with bronchogenic carcinoma. Our patient's hypokalemic alkalosis cannot be explained by any of the usual mechanisms evoking the loss of potassium. Of equal importance is the fact that our patient's blood and urine were both alkalotic—the paradoxical aciduria of potassium depletion was absent. An intracellular migration of potassium cannot be ruled out to explain the low serum potassium.

In table 1 the reported cases of bronchogenic carcinoma with adrenal functional abnormalities are tabulated. Many of these were reported in conjunction with signs of Cushing's syndrome, namely, trunkal obesity, hypertension, hyperglycemia, purple striae and polycythemia. Several patients manifested hypokalemia or hypokalemic alkalosis, as shown in column 5. All of the cases had adrenal hyperplasia and/or metastases, except for Thorne's first patient. In this case no detailed microscopic study of the adrenal glands was presented. A possible common denominator in these cases is that all the bronchogenic carcinomas were of the anaplastic variety. Adrenal metastases seem an unlikely explanation of the cushingoid state, since 20 to 30% of patients with carcinoma of the lung show such metastases without functional adrenal abnormalities. It is of interest to note that in two patients (cases 8 and 10), aldosterone assays were performed and were within the limits of normal.

TABLE 1  
Carcinoma of Lung and Adrenal Functional Abnormalities

Reference	Age	Sex	Cushing-like Features	Electrolyte Abnormalities	Adrenal		Steroid Level
					Hyperplasia	Metastasis	
1. Thorne <sup>1</sup>	36	M	Present	Not stated	0	0	Elevated
2. Thorne <sup>1</sup>	45	M	Present	Slightly alkalotic	+	+	Elevated
3. Brown <sup>2</sup>	45	F	Present	Not stated	+	0	Not stated
4. Massachusetts General Hospital <sup>3</sup>	76	F	Present	Hypokalemic alkalosis	+	0	Elevated
5. Kovach and Kyle <sup>4</sup>	22	M	Present	Hypokalemic alkalosis	+	+	Elevated
6. White <sup>5</sup>	58	M	Absent	Hypokalemic alkalosis	+	+	Elevated
7. Spaulding et. al. <sup>6</sup>	56	M	Absent	Hypokalemic alkalosis	0	+	Elevated
8. Massachusetts General Hospital <sup>7</sup>	68	M	Absent	Hypokalemic alkalosis	+	0	Elevated
9. Metzler <sup>8</sup>	46	M	Absent	Hypokalemic alkalosis	+	0	Elevated
10. Present	45	M	Absent	Hypokalemic alkalosis	0	+	Elevated

## II. Hypercalcemia with Neoplastic Disease but without Bony Metastases:

*Case 2.* A 49 year old Philippine male had complained of a productive cough for several months before admission. Physical examination revealed a chronically ill male with signs of weight loss. Other important findings were râles over the right hemothorax and a liver palpable 4 cm. below the right costal margin. Chest film revealed a large abscess in the right midlung field. The lung lesion was proved by bronchoscopic biopsy to be bronchogenic carcinoma. Serum calcium ranged between 15.5 and 17.4 mg.%, phosphorus between 3.0 and 4.0 mg.%, with an alkaline phosphatase of 14.8 to 18.3 Bodansky units (normal range, 1.5 to 4.0 Bodansky units). The patient's bromsulfalein retention was 29% at 45 minutes. The elevation of alkaline phosphatase was thought to be due to liver metastases. Careful search of all the skeletal x-rays did not reveal any osteolytic lesions. During the hospital course a phosphate clearance test was performed. Our patient's phosphate clearance was 10.3 ml./min. (normal, 6.3 to 15.5 ml./min.);<sup>9</sup> creatinine clearance was 48 ml./min., uncorrected for body surface area; per cent tubular reabsorption of phos-

phorus, 85 (normal, 87 to 95%).<sup>9</sup> At necropsy no osteolytic lesions were found in the bones examined, large hepatic metastases were present, and the parathyroid glands were normal.

*Comment:* In the last two years we have seen 134 cases of bronchogenic carcinoma, and have studied the serum calcium in 104 patients. Of this group, only two patients had borderline elevations of these values, and both had bony metastases. Urinary calcium excretion was measured in approximately one third of this group and was normal.

The occurrence of hypercalcemia in two cases of bronchogenic carcinoma was first reported by Connor and co-workers<sup>10</sup> in 1956, and later that year Plimpton and Gellhorn<sup>11</sup> reported 10 similar cases, two of whom had bronchogenic carcinomas. It is of interest to note that in Connor's patients the hypercalcemia disappeared with the removal of the tumor and recurred with the appearance of metastatic disease. One may speculate about an unknown substance being elaborated by the tumor to cause this biochemical abnormality. This substance may increase calcium absorption from the gastrointestinal tract, as in sarcoid, it may bind calcium, causing a change in the dissociation of serum calcium usually found, or the tumor may elaborate a parathyroid-like hormone material. However, no such substance has been demonstrated to date.

### III. Hypoglycemia:

*Case 3.* A 57 year old Negro male with a hepatoma was admitted because of right upper quadrant swelling of a few months' duration. It was not until late in his disease that he manifested symptoms of hypoglycemia. Figure 2 shows the occurrence of these episodes, their symptomatology and response to glucose administration. During four episodes occurring in the hospital, his blood sugars ranged from 17 to 45 mg.%; with the administration of glucose, the patient sustained a rapid recovery from his acute symptomatology.

*Comment:* This patient's hypoglycemia may be classified as hepatic in origin, for autopsy revealed a huge liver, weighing 5,200 gm., almost completely replaced by hepatoma. Also, a glucose tolerance test done before the onset of the hypoglycemic episodes showed a sustained elevation, the type that is associated with far advanced liver disease.

In the course of a two-year period we have seen three patients with malignant disease exhibit profound hypoglycemia. Two of these patients had extensive liver disease due to primary liver tumors. The third was admitted because of vague abdominal pain, anorexia and a 15 pound weight loss. Physical examination revealed a very large right upper quadrant mass that was firm and nodular. Liver chemical tests were slightly deranged, and fasting blood sugars were 65 to 77 mg.%. A glucose tolerance test was normal, and liver biopsy revealed carcinomatous tissue. Late in his course the patient had two episodes of hypoglycemia, at which times his blood sugar determinations were 25 mg.%. At necropsy he was found to

have a large retroperitoneal tumor and a normal liver. Histologic sections of this tumor showed it to be a reticulum cell sarcoma.

Many tumors that have caused hypoglycemia originated in the retroperitoneal area, and most of these tumors have been classified as sarcomas.<sup>12, 13</sup> The exact reason for hypoglycemia is unknown, but one possible explanation is the production by the tumor of an insulin-like material. Recently, August and Hiatt<sup>14</sup> analyzed a fibrosarcoma removed from a patient suffering from recurrent episodes of hypoglycemia. While the patient's plasma did not reveal the presence of an excessive amount of insulin-like activity, the tumor

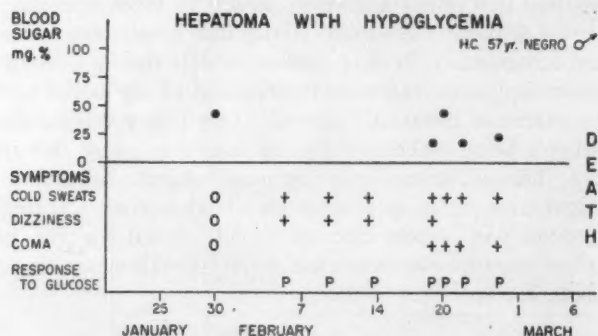


FIG. 2. Case 3. Graphic representation of clinical course. P = rapid disappearance of symptoms of hypoglycemia, dizziness, sweats and unresponsiveness. (See text.)

assays did. This is an intriguing speculation, one which seems more attractive than other possible explanations of this syndrome.

#### IV. Polycythemia:

*Case 4.* We were asked to see a 64 year old Negro female several months after a diagnosis of hypernephroma with metastases to the chest was made. At this time the patient's hematocrit was 62%; hemoglobin, 19.0 gm.%; white blood cell count, platelet count and reticulocyte count, normal. In retrospect, it was noted that during the preceding five months, several hemoglobin determinations had varied between 16.9 and 17.5 gm.%. White blood cell counts were all normal. During the ensuing three months the patient's hematocrit was greater than 60%, and later in her course she developed massive hematuria. At this time her hematocrit was within the limits of normal.

*Comment:* Polycythemia has been reported in association with both benign and malignant tumors.<sup>15, 16, 17</sup> In this clinical situation the polycythemia is not accompanied by leukocytosis or thrombocytosis, and the increased erythrocyte count returns to normal when the lesion is removed.

Again, no common denominator is apparent when one surveys the literature. It would be of great interest to assay the blood of these patients for erythropoietic activity, and to try to identify an erythrocytic substance from a tumor of this type. An important rule in evaluating any patient with

polycythemia is to make a careful search for a retroperitoneal tumor that may be the explanation of the disease process.

#### SUMMARY

Examples are given of mineralocorticoid abnormality, hypercalcemia, hypoglycemia and polycythemia associated with various malignant tumors, considered to be nonfunctioning by present definitions.

Careful appraisal of these clinical situations may help to shed light on the more basic bodily processes that these syndromes highlight.

#### ACKNOWLEDGMENTS

The authors would like to express their thanks to Dr. Fred Bartter, of the National Heart Institute, for performing the aldosterone assay, to Dr. Roy Hertz, of the National Cancer Institute, for the steroid determinations in case 1, and to Dr. Marcus Schaaf and Dr. Joseph Canary for the phosphate clearance test data of case 2.

#### SUMMARY IN INTERLINGUA

Es presentate un revista de plure phenomenos clinic observate in le presentia de tumores del genere appellate "non-functionante." Es reportate le caso de un patiente con anormalitate mineralocorticoide causate per un carcinoma pulmonar. In previemente reportate casos, anormalitates electrolytic e/o signos del syndrome de Cushing esseva observate con carcinomas microcellular del pulmon. Un meticulose scrutinio del presente caso e del casos trovate in le litteratura revela nulle denominator commun excepte le varietate anaplastic del primari carcinoma bronchogene.

Es reportate un caso de carcinoma pulmonar con hypercalcemia, sin metastases ossee. Iste patiente esseva studiate per medio de tests del clearance de phosphato e del reabsorption tubular de phosphoro. In ambe iste investigationes, le valores obtenite se trovava intra le limites del norma. Le necropsia revelava nulle lesiones osteolytic, e le glandulas parathyroide esseva normal. Es presentate un breve revista del litteratura concernite con le thema de hypercalcemia in le presentia de morbo neoplastic.

Es reportate in plus le caso de un patiente con hepatoma massive e hypoglycemia. Un patiente con sarcoma retroperitonee a cellulas reticular e hypoglycemia es mentionate.

Le quarte situation clinic discutite es illo de polycythemia associate con un hypernephroma. De accordo con le observationes in simile casos reportate per altere autores, iste patiente non habeva leucytosis o thrombocytosis associate con un augmento del massa erythrocytic. Es proponite que le seros e le tumores de iste patientes es examinate con respecto a lor activitate erythropoietic. Le litteratura pertinente relative a iste aspecto del problema es etiam passate in revista.

#### BIBLIOGRAPHY

1. Thorne, M. G.: Cushing's syndrome associated with bronchial carcinoma, *Guy's Hosp. Rep.* 101: 251, 1952.
2. Brown, H. W.: A case of pluriglandular syndrome: "diabetes of bearded women," *Lancet* 2: 1022, 1928.
3. Case records of the Massachusetts General Hospital, weekly clinicopathological exercises, *New England J. Med.* 248: 29, 1953.
4. Kovach, R. D., and Kyle, L. H.: Cushing's syndrome and bronchogenic carcinoma, *Am. J. Med.* 24: 981, 1958.

5. White, A. G.: Diabetes insipidus associated with edema, *New England J. Med.* **250**: 633, 1954.
6. Spaulding, W. B., Oille, W. A., and Gornall, A. G.: Mineralo-corticoid-like disturbance associated with adrenal metastases from a bronchogenic carcinoma, *Ann. Int. Med.* **42**: 444, 1955.
7. Case records of the Massachusetts General Hospital, weekly clinicopathological exercises, *New England J. Med.* **259**: 1128, 1958.
8. Metzler, C., and Flink, E. B.: Adrenal cortical hyperfunction associated with metastatic bronchogenic carcinoma, *Journal Lancet* **76**: 242, 1956.
9. Kyle, L. H., Schaaf, M., and Canary, J. J.: Phosphate clearance in the diagnosis of parathyroid dysfunction, *Am. J. Med.* **26**: 240, 1958.
10. Connor, T. B., Thomas, W. C., Jr., and Howard, J. E.: The etiology of hypercalcemia associated with lung carcinoma, *J. Clin. Investigation* **35**: 697, 1956.
11. Plimpton, C. H., and Gellhorn, A.: Hypercalcemia in malignant disease without evidence of bone destruction, *Am. J. Med.* **21**: 750, 1956.
12. Scholz, D. A., Woolner, L. B., and Priestley, J. T.: Spontaneous hypoglycemia associated with fibrogenic tumor: report of two cases, *Ann. Int. Med.* **46**: 796, 1957.
13. Silvis, R. S., and Simon, D. S.: Marked hypoglycemia associated with nonpancreatic tumors, *New England J. Med.* **254**: 14, 1956.
14. August, J. T., and Hiatt, H. H.: Severe hypoglycemia secondary to a nonpancreatic fibrosarcoma with insulin activity, *New England J. Med.* **258**: 17, 1958.
15. Conley, C. L., Kowal, J., and D'Antonio, J.: Polycythemia associated with renal tumors, *Bull. Johns Hopkins Hosp.* **101**: 63, 1957.
16. DeMarsh, Q. B., and Warmington, W. J.: Polycythemia associated with renal tumor, *Northwest Med.* **54**: 976 (Sept.) 1955.
17. Lawrence, J. H., and Donald, W. G., Jr.: Polycythemia and hydronephrosis or renal tumor, *Ann. Int. Med.* **50**: 959, 1959.

# THE DIAGNOSIS AND CLASSIFICATION OF MEDIASTINAL MASSES. 1. A STUDY OF 782 CASES \*

By HAROLD A. LYONS, F.A.C.P., *New York, N. Y.*, GEORGE L. CALVY, F.A.C.P., Captain (MC) USN, *St. Albans, N. Y.*, and BILLY P. SAMMONS, M.D., Lieut. Comdr. (MC) USN, *Pensacola, Florida*

THE problem posed by the discovery of a mediastinal mass is becoming of more frequent concern to the physician. Widespread employment of the routine chest roentgenogram in various surveys and in the military service has increased the number of mediastinal masses discovered during asymptomatic stages, and has shown them to be more frequent than the literature indicates. This report is based on an experience with 782 mediastinal masses.

Previously, lesions of the mediastinum were either passively observed or treated by radiation, without benefit of a specific diagnosis.<sup>1-3</sup> More recently, the attitude has been to perform early surgery to facilitate the

TABLE 1

Location of Tumors and Cysts in the Mediastinum<sup>a</sup>

Anterior Mediastinum	Middle Mediastinum
Thymoma	Bronchogenic cyst
Teratoma	Lymphoma
Goiter	Pericardial cyst
Parathyroid adenoma	Plasma cell myeloma
Lymphoma	
Lipoma	Posterior Mediastinum
Fibroma	Neurilemmoma
Lymphangioma	Neurofibroma
Hemangioma	Ganglioneuroma
Chondroma	Sympathicoblastoma
Thymic cyst	Fibrosarcoma
Rhabdomyosarcoma	Lymphoma
	Goiter
Superior Mediastinum	Xanthofibroma
Goiter	Gastroenteric cyst
Bronchogenic cyst	Chondroma
Parathyroid adenoma	Myxoma
Myxoma	Meningocele
Lymphoma	Paraganglioma

\* Received for publication May 12, 1958.

Presented in part as a Morning Lecture at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, May 2, 1958.

From the Department of Medicine, State University of New York, College of Medicine, Downstate Medical Center, and the Departments of Medicine and Radiology and Medicine, U. S. Naval Hospital, St. Albans, N. Y., and the Second Pulmonary Disease Division, Kings County Hospital Medical Center, Brooklyn, N. Y.

The opinions expressed herein are those of the authors, and do not necessarily reflect the views of the Navy Department.

Requests for reprints should be addressed to Harold A. Lyons, M.D., Professor of Medicine, State University of New York, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn 3, N. Y.

diagnosis and, if possible, the removal of these lesions. This approach is more productive than the former, but the injunction that thoracotomy be performed under any circumstance has led to the omission of certain valuable diagnostic measures, and surgery is sometimes performed unnecessarily. It is proper to consider this group of patients as having mediastinal *masses*, because cysts, tumors and cardiovascular abnormalities often present similar clinical manifestations. It is also important to differentiate these abnor-

TABLE 2  
Diagnostic Procedures

A. Roentgenographic Studies:

1. Posterior-anterior stereoscopic and lateral chest roentgenograms
- \*2. Fluoroscopy
3. Potter-Bucky grid films
4. Supervoltage roentgenograms
5. Tomograms
6. Esophagrams
7. Kymograms
- †8. Angiocardiograms
9. Retrograde angiograms
10. Barium visualization of gastrointestinal tract
11. Bronchograms
12. Myelograms
13. Diagnostic pneumothorax and pneumoperitoneum

B. Surgical Procedures:

1. Bronchoscopy
- †2. Scalene node biopsy
3. Biopsy:
  - a. Abnormal nodes
  - b. Liver
  - c. Pleura
  - d. Other tissues
- ‡4. Thoracotomy
5. Thoracentesis

C. Miscellaneous:

1. Skin tests for specific granulomas
2. Sputum studies for organisms and malignant cells
3. Tracer dose of radioactive iodine
4. Slit lamp examination for sarcoid granuloma
5. Bone marrow studies

\* This diagnostic study is most valuable and may often detect a tumor vaguely seen by other methods. It will also show characteristic helpful signs.

† The most definitive and valuable special procedures, often precluding further examination.

‡ Final diagnostic study, often curative, the use of which must not be delayed in indeterminate lesions of the mediastinum.

malities as malignant or benign, or as vascular masses, and to determine whether removal gives a prospect of cure. If this is done, some patients may be spared unnecessary surgery.

The great majority of our patients have been in the younger age group. The usual time of discovery is at a routine chest roentgenographic study. This is often a stage when surgical cure may still be attainable. Symptoms caused by displacement and compression of adjacent structures may pro-

vide the initial evidence of mediastinal disease. Fullness and tightness in the chest are usual manifestations. A mediastinal neoplasm present from birth may not give any clue of its presence, and pressure symptoms may not develop until the third or fourth decade of life. On the other hand, the pressure symptoms in early life may be so agonizing as to require immediate relief. Eventually, pain may occur; this may be localized, referred or wide-

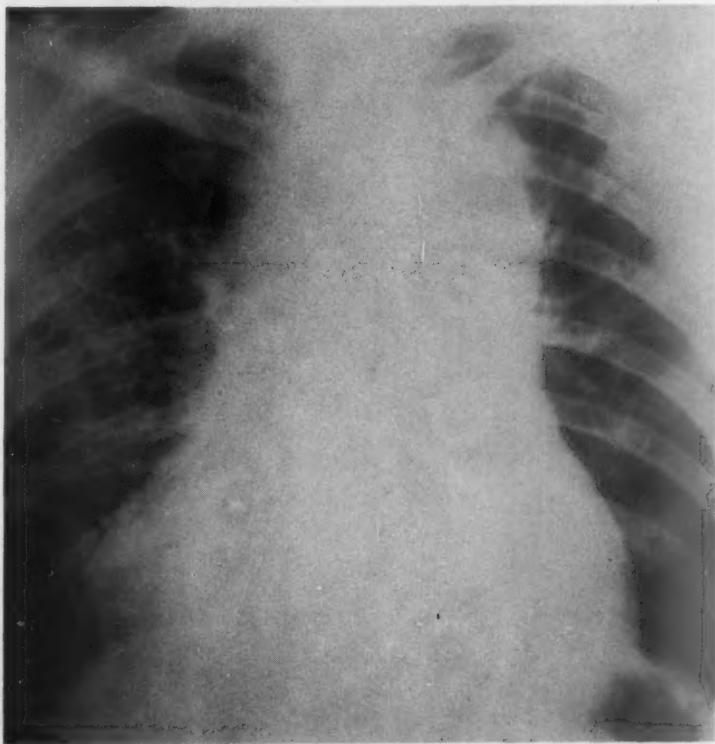


FIG. 1. This is the posterior-anterior chest roentgenogram of a 26 year old white man admitted with substernal pain aggravated by exercise, and palpitation and dyspnea on exertion. The physical examination showed substernal dullness and a pericardial friction rub. The film of the chest shows a massive tumor projecting into both the right and the left chests. No nodes were found. A scalene node biopsy gave definite evidence of lymphoblastoma.

spread, and either dull or sharp in character. Pressure on the trachea may cause wheezing and dyspnea, as will pressure on a bronchus; segmental or lobar atelectasis may result. Dyspnea may be a prominent complaint, especially with a rapidly growing tumor, and may be completely out of proportion to the size of the mass.

Although the original mass is detected by the roentgenographic exam-

ination, there are supplemental procedures which are most useful. Their choice and use are dictated by the circumstances. Additional roentgenographic procedures are outlined in table 2. Two procedures, (1) *the scalene node biopsy*, and (2) *angiocardiology*, have solved certain prob-

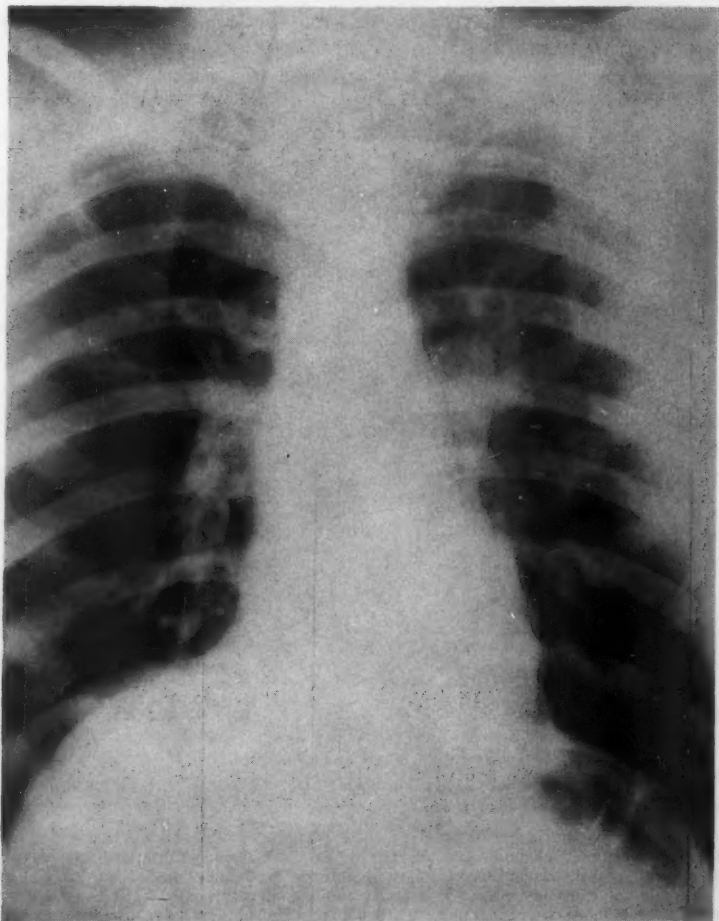


FIG. 2. The roentgenogram after radiation, showing regression of the mass except for a residual slight widening of the superior mediastinum and the left hilar area.

lems, and have led to the avoidance of unnecessary or premature operations. Scalene node biopsy has been sufficiently helpful in a significantly high percentage of patients to warrant its routine use.<sup>4-8</sup> Its greatest value has been in lymphomas, certain granulomas, and mediastinal or pulmonary tumors. Angiocardiology has reduced the number of instances in which

thoracotomy is necessary for the diagnosis of a noncorrectable vascular lesion. Aneurysms, coarctation and cardiac abnormalities are examples.<sup>9-12</sup>

By means of angiocardigraphy, not only may mediastinal tumors be outlined, but their relations to adjacent cardiovascular structures may also be clearly defined. This is of tremendous significance both in estimating the operability of a given tumor and in aiding the surgeon to avoid certain

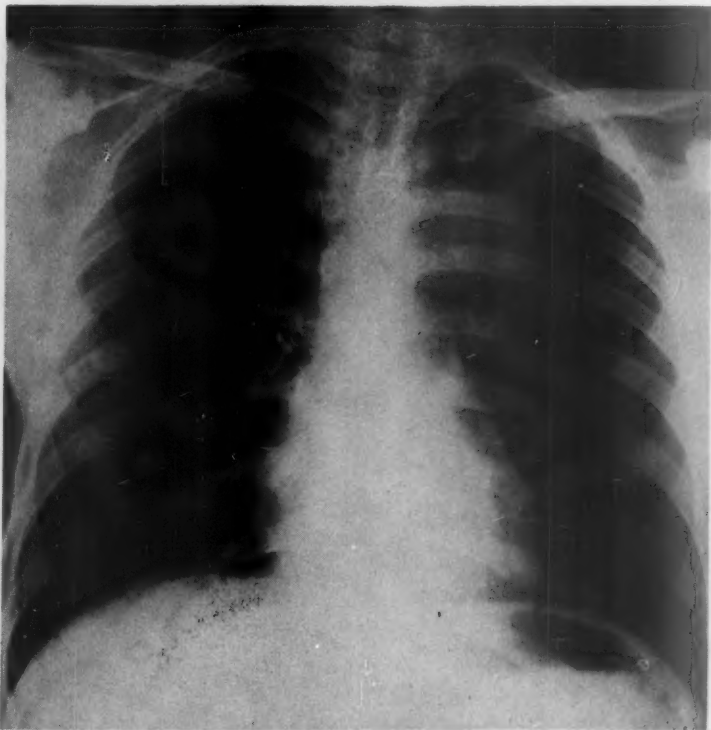


FIG. 3. This is the posterior-anterior chest roentgenogram of a 34 year old Negro male. There is a large nodular density in the aortic knob region. Neither symptoms nor physical findings were present. The laboratory studies were normal. On angiocardigraphic examination the mass was shown to be avascular. A scalene node biopsy was non-diagnostic. Exploratory thoracotomy was performed, and a large nodal mass was found wrapped about the aortic arch and intimately adherent to the mediastinal structures. Histologically, this was Hodgkin's disease.

complications. It is safe to say that the most decisive single factor in the successful extirpation of a mediastinal tumor is its separation from the large vessels or parts of the heart with which it may be in intimate contact. It is this element in the operation which causes the most concern to the surgeon. Indeed, hemorrhage secondary to accidental entry into a large vessel or one of the atria is responsible for a large proportion of the operative mortality.

*In the examination of all mediastinal masses it is absolutely necessary to make a contrast examination of the esophagus, even though the medical history fails to record symptoms attributable to the esophagus. The x-ray study not infrequently reveals a shift of the esophagus, or demonstrates the impressions on the esophageal lumen by glands or vessels. It may also demonstrate an unsuspected achalasia of the esophagus as the cause of the mediastinal abnormality.*



FIG. 4. The lateral film showing the middle mediastinal location of the tumor mass.

The vast majority of mediastinal enlargements require thoracotomy for positive diagnosis,<sup>1, 2, 4, 18-18</sup> even though many significant clinical clues and past experience may suggest the correct diagnosis. If other diagnostic studies fail to establish a specific diagnosis, exploratory thoracotomy should be undertaken. *Procrastination does not serve the best interests of the patient.* Curreri and Gale state that clinical manifestations and radiologic studies permit an accurate diagnosis in at least 80% of the mediastinal

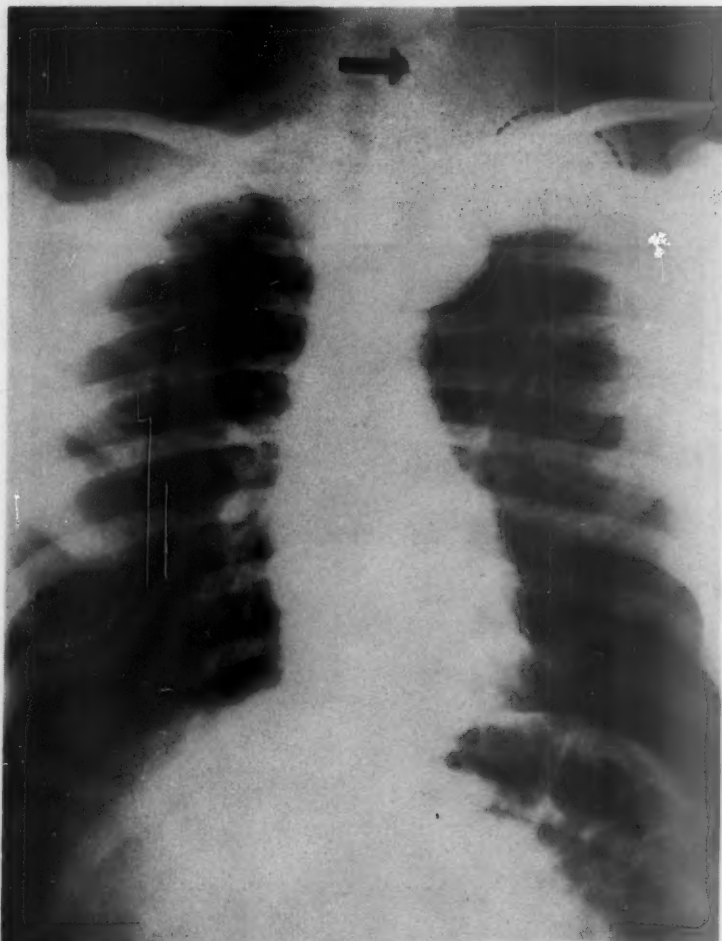


FIG. 5. The posterior-anterior chest roentgenogram of a 19 year old white male who had a progressive paraplegia, with greater involvement of the left side. There is a large, smooth density in the left superior mediastinum. In addition to the mediastinal mass, soft tissue densities are to be noted in the left apical inlet and cervical region. These areas are outlined by dotted lines in the figure. Because of the seriousness of the condition of the patient, an immediate thoracotomy and cervical laminectomy were done, and multiple neurofibromata were removed. The patient was relieved of his paralysis, and after a prolonged convalescence returned to normal activity.

lesions.<sup>17</sup> The location, definition, size, shape and relative density of a roentgenographic shadow, and the demonstration of air, bone and calcification of teeth within its confines, are of diagnostic significance. If the roentgenographic studies show destructive invasion of bone, malignancy is strongly suggested. However, benign tumors of nervous tissue origin and

aneurysms may show compression erosions of adjacent vertebrae, sternum or ribs.

By the division of the mediastinum into anterior, middle and posterior portions, some types of tumors and cysts tend to be found in a specific compartment of the mediastinum. In the *anterior mediastinum*, between the sternum anteriorly and the trachea, bronchi and the great vessels posteriorly, and extending upward to the neck, teratoderoids, cysts, thymomas, thyroid



FIG. 6. The appearance of the dumbbell-shaped neurofibromata which were removed. Although usually single, rarely these neurogenic tumors are multiple.

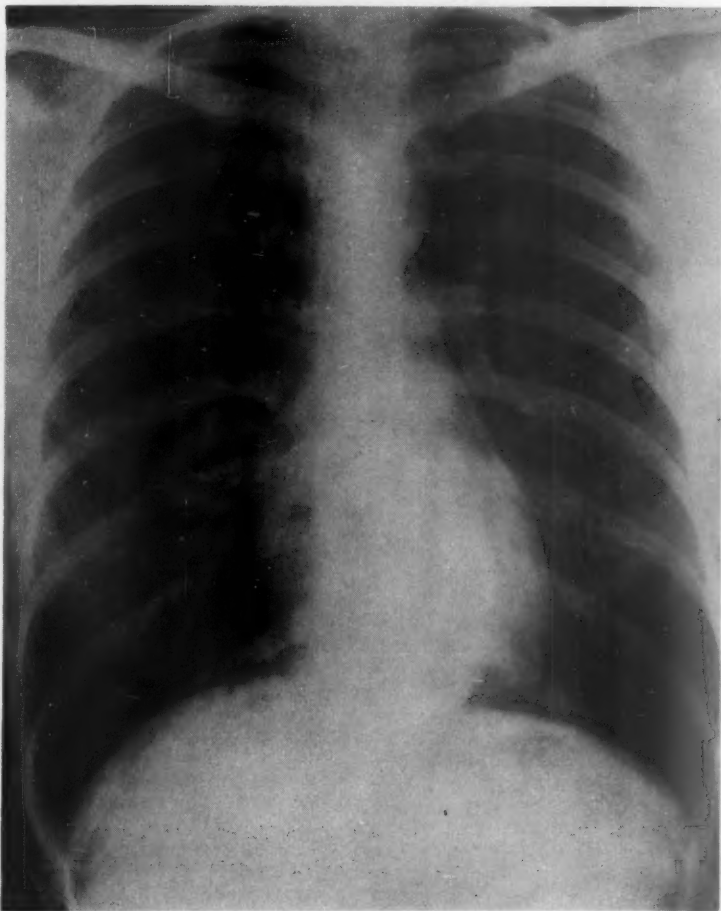


FIG. 7. This is the anterior-posterior chest roentgenogram of a 24 year old housewife who had an upper respiratory infection. An abnormal mass is noted in the retrocardiac area, which is vertically fusiform in outline and posterior in location. A sympathetic neurogenic tumor was diagnosed. This patient illustrates the area where abnormalities on a roentgenogram may be missed. Thoracotomy demonstrated a ganglioneuroma, which was completely removed.

and parathyroid adenomas and hyperplasia are most common. The *middle mediastinum* is the usual site or origin of bronchogenic and gastroenteric cysts and lymphomas, and of metastatic, malignant and granulomatous lesions.

In the *posterior mediastinum*, tumors of neural origin predominate. Differential diagnosis is further aided by a knowledge of the age distribution and sex frequency for each type of mediastinal mass.

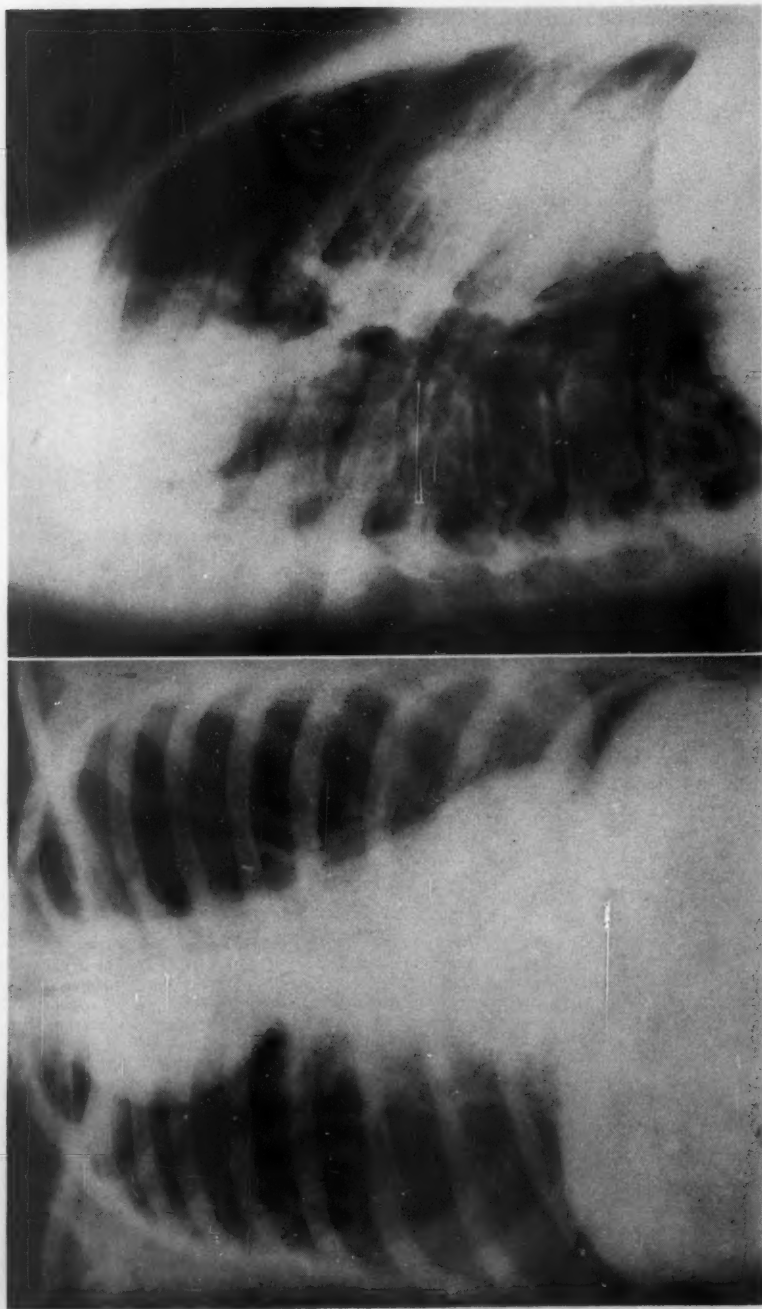


FIG. 8. (left) The posterior-anterior chest roentgenogram of a 32 year old male who complained of frequent colds, with one episode of hemoptysis. A large density with a smooth border extension from the right superior mediastinum. On fluoroscopy the density was noted to change size on respiration, becoming larger on inspiration.

FIG. 9. (right) The right lateral roentgenogram of the chest, showing the density to be present in the superior and posterior mediastinum, a characteristic location for a bronchogenic cyst. Thoracotomy was done and a large cyst was removed. This contained a mucoid type of material, and was lined with a columnar ciliated epithelium. The diagnosis was a bronchogenic cyst.

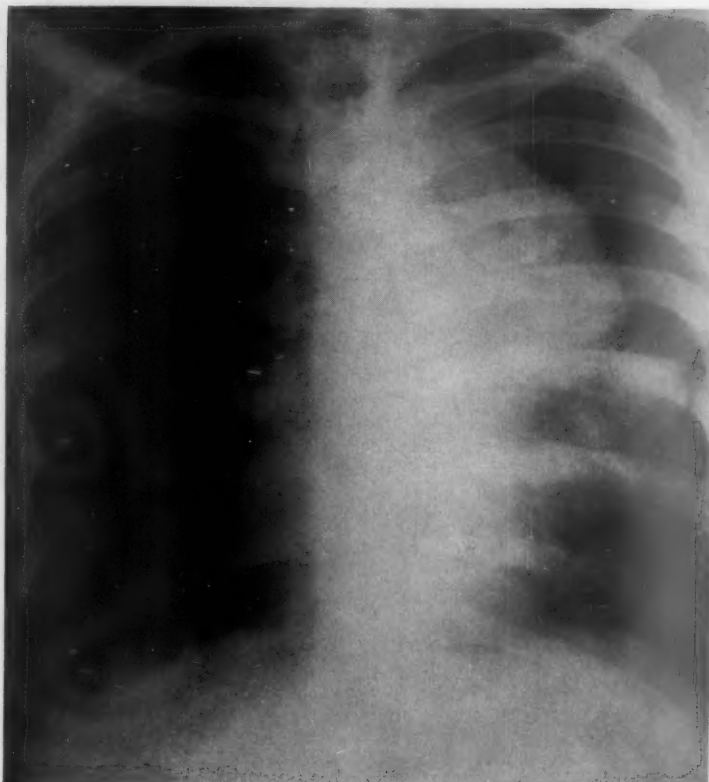


FIG. 10. The posterior-anterior chest roentgenogram of a 29 year old white male, showing a large mediastinal density extending from the left mediastinum laterally. There was a separate, rounded lesion at the inferior margin of the main density. Four months previously his chest film had been normal. At this time there were a dry cough and substernal aching during the night. Physical examination was normal. This represents a mediastinal tumor with a "satellite lesion" which is pathognomonic of a malignant teratodermoid.

Tumors which arise in the chest wall near the anterior or posterior mediastinum are classified as mediastinal tumors, although their origin is actually extramediastinal. In the superior portion of the mediastinum, lesions of the neck may encroach upon the mediastinum. Neoplasms of distant organs may first become manifest as metastases to mediastinal structures.

The location of tumors and cysts of the mediastinum are shown in table 1.<sup>3</sup> The published reports do not reflect the true frequency of a given tumor encountered at operation or autopsy.

*Lymphomas* (203 cases): Bilateral enlargement of the mediastinum may be a finding that is due to lymphomatous disease. This radiologic

manifestation demands a careful search for palpable lymph nodes. If none is found, scalene node biopsy is required. Unilateral mediastinal enlargement does not exclude the diagnosis of lymphoma, and the same biopsy procedure must be followed. That scalene node biopsy should be done by an experienced surgeon is emphasized by the increased proportion of positive biopsies obtained by the skilled surgeon. In the absence of other available material for biopsy, a scalene node biopsy gave a positive diagnosis in 92% of the lymphomas.

In the group of patients seen at the U. S. Naval Hospital, the lymphomas were the tumors most commonly found. There were 146 cases of Hodg-



FIG. 11. The lateral roentgenogram, showing the massive anterior mediastinal mass displacing the mediastinal structures posteriorly. On exploratory thoracotomy a highly invasive and very vascular teratocarcinoma was found. About 30% of teratodermoids are malignant.

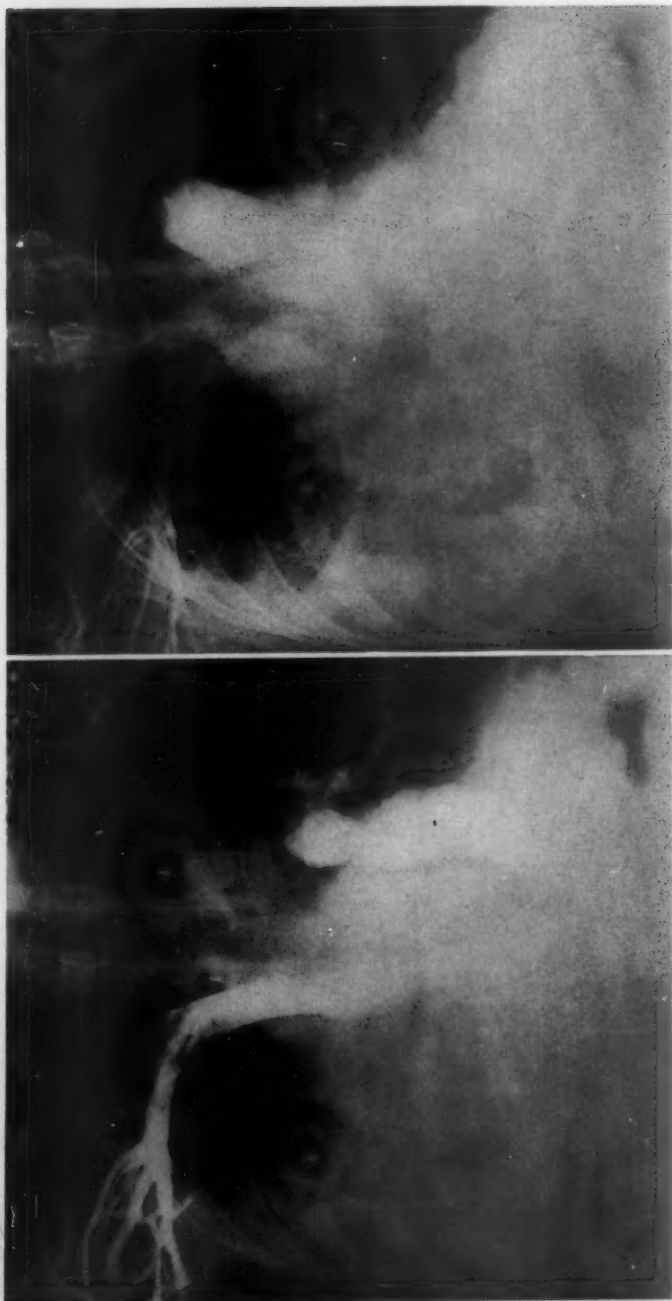


FIG. 12. A. (*left*) This is the posterior-anterior angiographic study of a 56 year old Negro female who had marked fever and dyspnea. One is able to note the large mass in the right with a fluid collection and partial occlusion of the right pulmonary artery. B. (*right*) This film, when the left side of the circulation is opacified, demonstrates avascularity.



FIG. 12C. The lateral angiogram, showing the displacement posteriorly by the anterior mass, with partial obstruction of the right pulmonary artery. On removal, this mass was a dermoid cyst which had ruptured, spilling sebaceous material into the pleural cavity.

kin's disease, 40 cases of lymphosarcoma, eight cases of reticulum cell sarcoma and 14 cases of Brill-Symmers disease.

The incidence of mediastinal masses discovered by routine chest roentgenography in asymptomatic individuals; and in those having chest pain, dyspnea and weight loss, was approximately the same. The symptoms were strikingly similar to those described in pulmonary tuberculosis; fever,

weight loss, fatigue and night sweats were often the complaints. The majority of diagnoses of mediastinal lymphomas were made by biopsy of cervical lymph nodes or scalene node biopsy.

When the diagnosis is established, consideration of treatment is governed by the extent of the disease. The neoplastic process may be limited to the mediastinum or may involve other organs and tissues. In the latter instances treatment with radiation or the nitrogen mustard compounds will be advised. In the first instance, where there was a localized mass, surgical removal was the preferred method of treatment. Later experience indicates that intensive radiotherapy is the best method.<sup>19-21</sup>

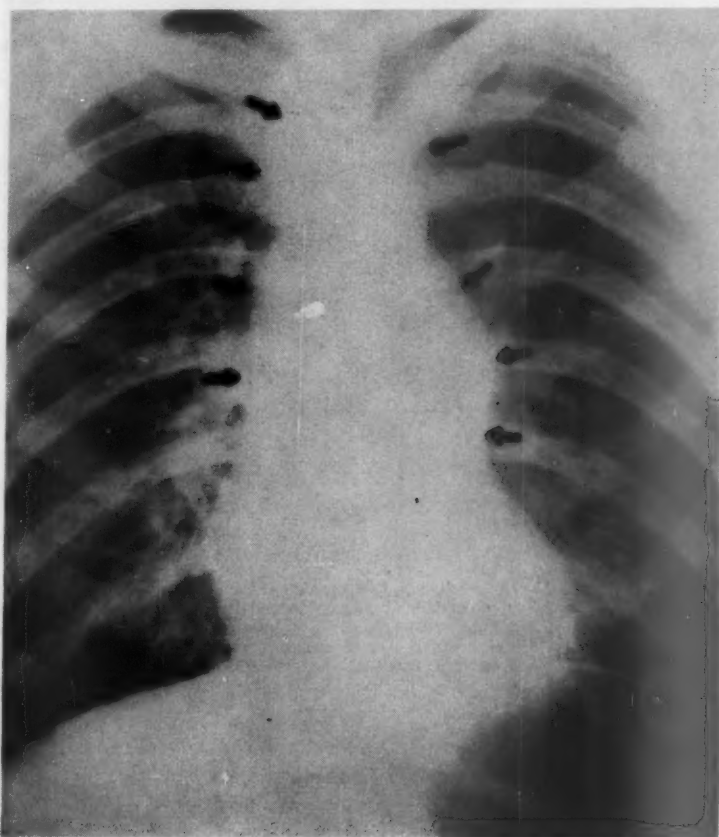


FIG. 13. The posterior-anterior roentgenogram of the chest of a 21 year old male whose only complaint was a mild dyspnea on exertion. A large, dense mass occupies the superior mediastinum, which blends with the cardiovascular silhouette (outlined by arrows). This is a good example of how some mediastinal masses can be undetected on a routine posterior-anterior chest roentgenogram. This abnormality was not interpreted by readers of previous chest roentgenograms.



FIG. 14. The lateral view roentgenogram, showing the mass to be in the posterior-superior mediastinum. It is better defined as an abnormality on this x-ray examination. On exploratory thoracotomy, this proved to be a thymic cyst. Although considered to be rare in most reports, 12 were found in this group. Another unusual feature was the location of this cystic tumor in the posterior mediastinum. The usual position for thymomas is the anterior mediastinum, but we have noted several in the posterior mediastinum.

*Neurogenic Tumors* (15 cases): The diagnosis of neurogenic tumors is suggested by the appearance in the posterior mediastinum of a sharp, round, dense shadow. Occasionally, these tumors may be discovered in the anterior or in the middle mediastinum. Rarely, they may be so large as to present in the superior, posterior, middle and anterior mediastinum; when they present in these areas, they may resemble thyroid tumors or bronchogenic cysts. The large size may lead to an erroneous clinical diagnosis of bronchogenic carcinoma in older patients. Like other mediastinal masses, neuro-

genic tumors may be behind the heart and appear indistinctly on routine chest films.

These tumors at times may arise from nerve roots within the spinal canal, grow through the intervertebral foramina, and continue to increase in size within the mediastinum. Because of their shape, such lesions are labeled "dumbbell" or "hourglass" tumors. The radiologic detection of enlarged vertebral foramina in association with the mediastinal density is a helpful aid to diagnosis.

These characteristics are found in all of the benign neurogenic tumors, neurilemmomas and neurofibromas. Ganglioneuromas arise at the site of the sympathetic chains and, although benign, are highly invasive. They occur in younger patients. Neuroblastomas are malignant and may metastasize, especially to the bones. When bony lesions without pulmonary metastases (which are extremely rare) occur with a posterior mediastinal tumor, the diagnosis of neuroblastoma is suggested.

Tumors taking origin from the sympathetic and peripheral nerves are not common. Paragangliomas and pheochromocytomas are rare. The neurofibromas may occasionally be malignant.

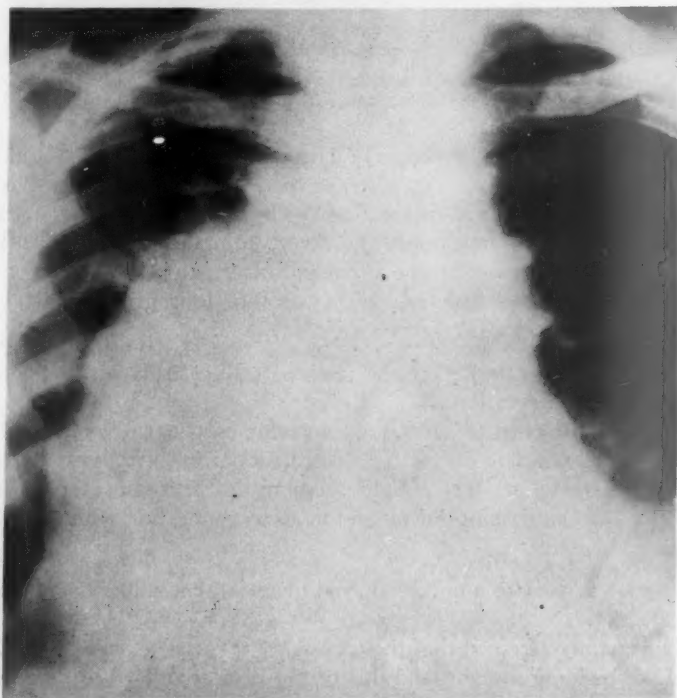


FIG. 15. The posterior-anterior roentgenogram of the chest of a 22 year old male who had marked symptoms of dyspnea and other signs of mediastinal compression.

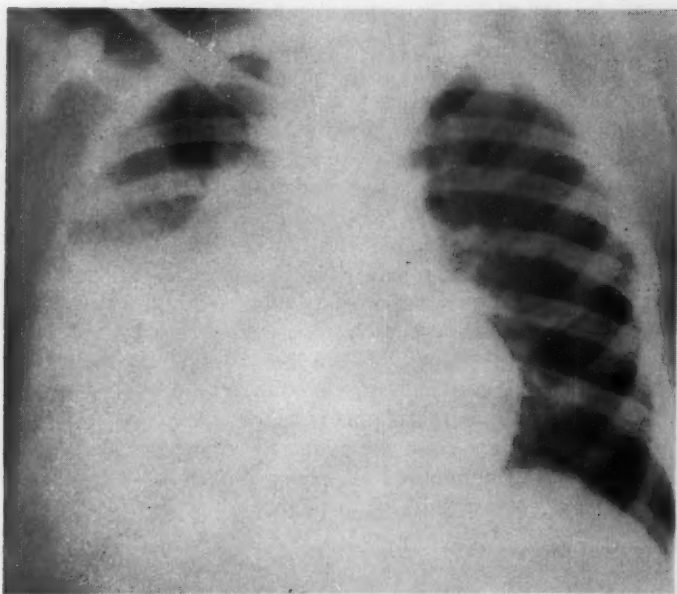


FIG. 16. Another film taken three weeks later, when the patient suddenly experienced a shock-like episode and the development of the right-sided pleural effusion.

*Bronchogenic Cysts* (two cases) : These tumors are not rare and, characteristically, most occur in the posterior part of the superior mediastinum at the level of the tracheal bifurcation. They may be asymptomatic and be an incidental finding at autopsy; however, in infancy and early childhood they may produce signs of tracheobronchial obstruction.

Maier has classified bronchogenic cysts into four groups on the basis of their location: <sup>22</sup>

1. *Paratracheal*: attached to the tracheal wall, usually on the right just above the bifurcation.
2. *Carinal*: attached to carina and anterior esophageal wall.
3. *Hilar*: attached to one of the main or lobar bronchi.
4. *Para-esophageal*: in intimate relationship with the esophagus, and may even be within its wall and have no connection with the tracheobronchial tree.

The cysts are filled with a milky, mucoid material that contains desquamated epithelial cells.

It is generally accepted that these cysts <sup>18, 22-26</sup> arise as embryonic derivations of the budding foregut, and this origin is in accord with their location. Maier also advances a possible interrelationship with tracheal diverticula and tracheo-esophageal fistulas.

These cysts may be mistaken for neurogenic, dermoid and pericardial cysts, as well as intrathoracic goiters. The tumor may move on swallowing, and may occasionally be palpated in the neck as a smooth, soft mass. A sudden increase in size may cause dyspnea, dysphagia and venous obstruction. Hemoptysis is a sign that infection has occurred. These lesions may also be overlooked when they occur behind the heart, and for this reason overpenetrated Bucky films and lateral films are needed.

*Teratoderms* (35 cases): This is the most common anterior mediastinal tumor, and thus should be the first to be considered when an abnormal roentgenographic shadow is discovered in this area. It occurs rarely in the posterior mediastinum (twice in our experience).

Representing one of the most interesting lesions of the mediastinum, teratoderms occur in early life and have an equal sex distribution. About 30% show malignant changes. This tumor is usually found on the routine



FIG. 17. Three days after the film shown in figure 16, when at another hospital a thoracentesis was done and air was inadvertently allowed to enter the pleural space. The fluid obtained was bloody. This patient died three days later, and on postmortem examination a large, malignant teratodermoid was found which had eroded and perforated the aorta just above the aortic valves.

roentgenogram. When it contains calcium or bone, a specific diagnosis can be made. Pain in the chest, dyspnea and cough are the presenting symptoms, and are due to pressure on neighboring structures. Although hair in the sputum is frequently described as a characteristic finding, it is extremely rare. As the tumor enlarges, vena caval obstruction results. Symptoms and signs are late manifestations. The discrepancy between the absence of clinical symptoms and the objective finding of an anterior mediastinal mass suggests the diagnosis of dermoid cyst or teratoma.

In the military service these lesions are discovered on routine radiologic examination, whereas in civilian practice the patient comes to attention be-

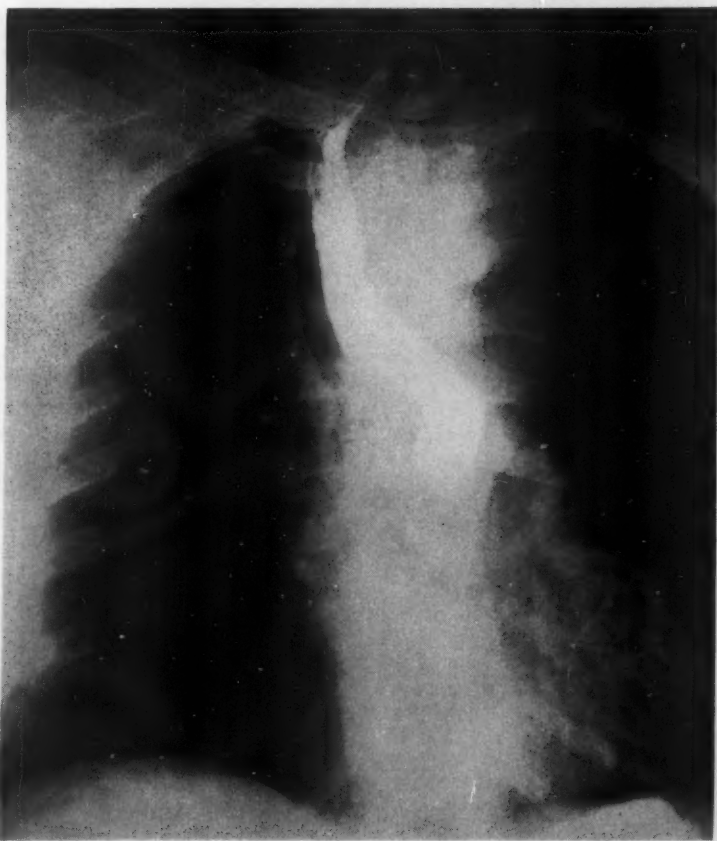


FIG. 18. The barium-esophageal roentgenogram of a 62 year old white female who had noted occasional episodes of difficulty in swallowing for the last six years. Within the last six months there had been exertional dyspnea. On physical examination a nodular thyroid was palpated, and a mass which, on swallowing, rose from the retromanubrial space. A radiiodine uptake over the sternal area gave marked activity, which was interpreted as evidence of active intrathoracic thyroid tissue.

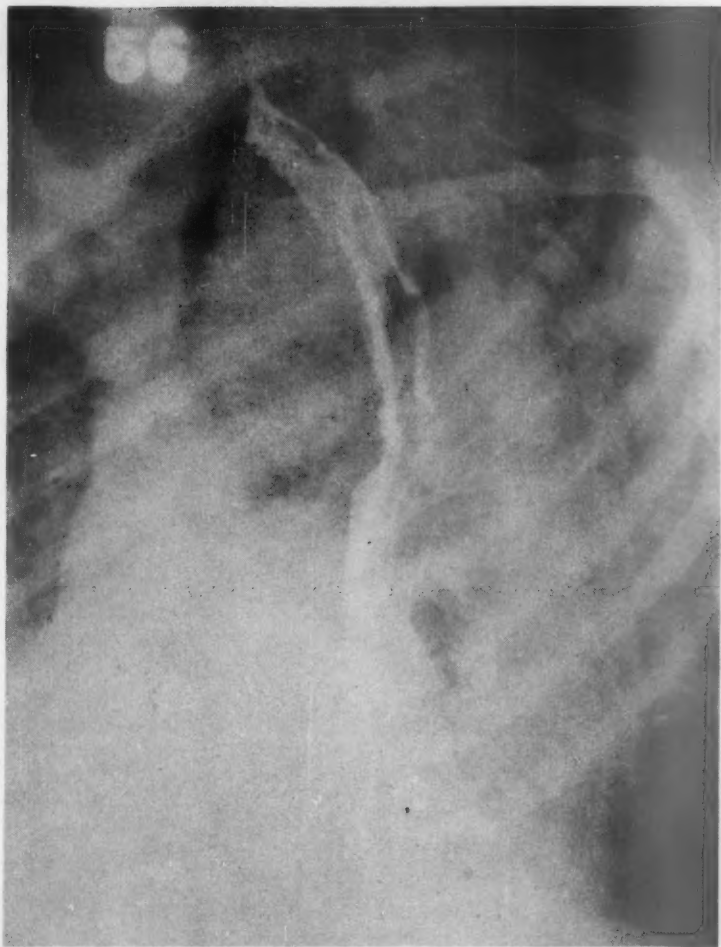


FIG. 19. A left anterior oblique barium swallow x-ray study, showing the large anterior density. The mass is displacing the esophagus posteriorly and the trachea anteriorly. Removal was accomplished by a cervical approach.

cause of symptoms. Accordingly, the presence of symptoms in this latter group is more usual.

An anterior ovoid mass with a sharply defined border is highly suggestive of a teratodermoid. The border may be partially or totally obscured by atelectasis, pneumonitis or pleural effusion. This may confuse the unwary. It has been reported as an intrapericardial tumor, which may cause even greater difficulty in diagnosis.<sup>27</sup>

It is presumed by pathologists that these tumors are present from birth,

but grow to considerable size only during adolescence and later life. Elements of tissue arising from germ layers other than ectoderm have been noted.<sup>3</sup>

If serial chest roentgenograms show a rapid rate of growth, the tumor is almost certainly malignant. A sudden increase in size within a few days is usually a sign of hemorrhage or infection within the tumor. The recognition of satellite spheroid densities on the chest roentgenogram is invariably a finding associated with advanced malignant tumors.

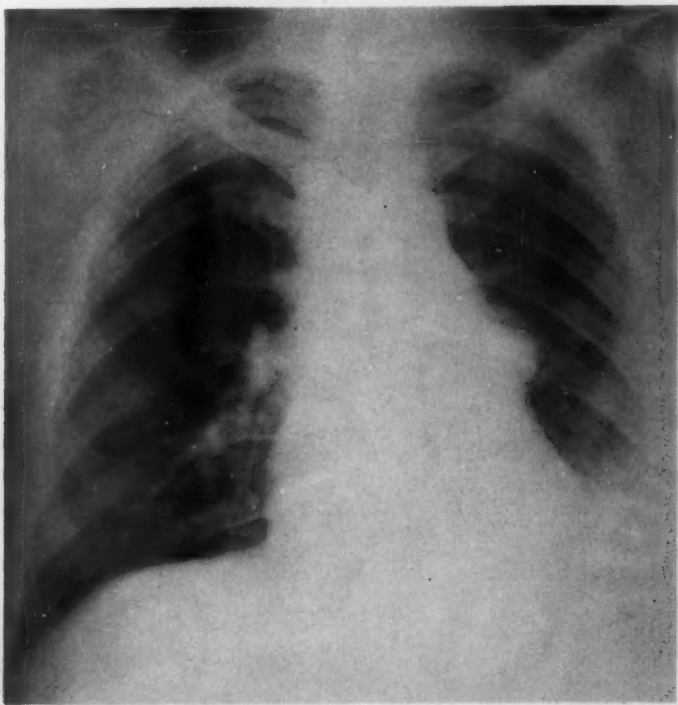


FIG. 20. The posterior-anterior x-ray examination of a 32 year old barber who, because of slight fever and cough, was admitted to the hospital. The roentgenographic study shows a rounded prominence of the left cardiac border and a left-sided pleural effusion.

*Thymomas* (26 cases): Thymomas may be solid tumors, benign or malignant. They are usually highly invasive tumors, but may be encapsulated. Recurrence is not uncommon, even with tumors thought to be completely removed by surgery. In our experience, cysts occur not infrequently, although most observers state that thymic cysts are rare.<sup>3, 15, 18</sup> Twelve of the mediastinal masses in the series were classified as thymic cysts. Hemorrhage within the cyst may cause sudden enlargement and onset of symptoms.

In malignant thymomas, symptoms are usually prominent: fever, substernal pain, cough and weight loss. Patients with these and other anterior mediastinal tumors may complain of angina, and may have electrocardiographic changes simulating a myocardial infarction due to interposition of tumor between chest wall and heart. Angiocardiography has been a distinct



FIG. 21. The lateral roentgenographic study shows the abnormal density to be in the anterior mediastinum (outlined by arrows). The abnormal density and the pleural effusion disappeared spontaneously. There have been three cases of mediastinal effusion similar to this example and simulating a mediastinal tumor. Only one was present in a patient with congestive heart failure. All absorbed spontaneously.

aid in showing the location, extent and vascular invasion of the tumor, and demonstrates the avascularity of this neoplasm.

None of our patients exhibited myasthenia gravis. Symptoms, however, may not appear for years after the detection of the tumor.<sup>28-30</sup> This may explain the absence of myasthenia gravis in our patients. The removal of the tumor has not consistently relieved the symptoms.

*Intrathoracic Goiter* (20 cases): An aberrant location of the thyroid was not uncommon in producing an upper mediastinal mass in this series. Crile<sup>31</sup> reported an incidence of 0.8% in 11,800 thyroidectomies. It is considered that the intrathoracic tumor is merely an extension of the thyroid tissue downward and anterior to the esophagus and trachea. Rarely, the extension arises from the posterior portions of the lobe and then proceeds posteriorly to the trachea and esophagus. The posterior disposition was emphasized by Lahey<sup>32</sup> and Sweet<sup>33</sup>; von der Lieth and Lester<sup>34</sup> found less than 40 reported instances of this type.

Most patients are asymptomatic, but some may suffer substernal distress, dyspnea, or even stridor and respiratory embarrassment.

Intrathoracic thyroid enlargement is suggested by (1) a mass in the

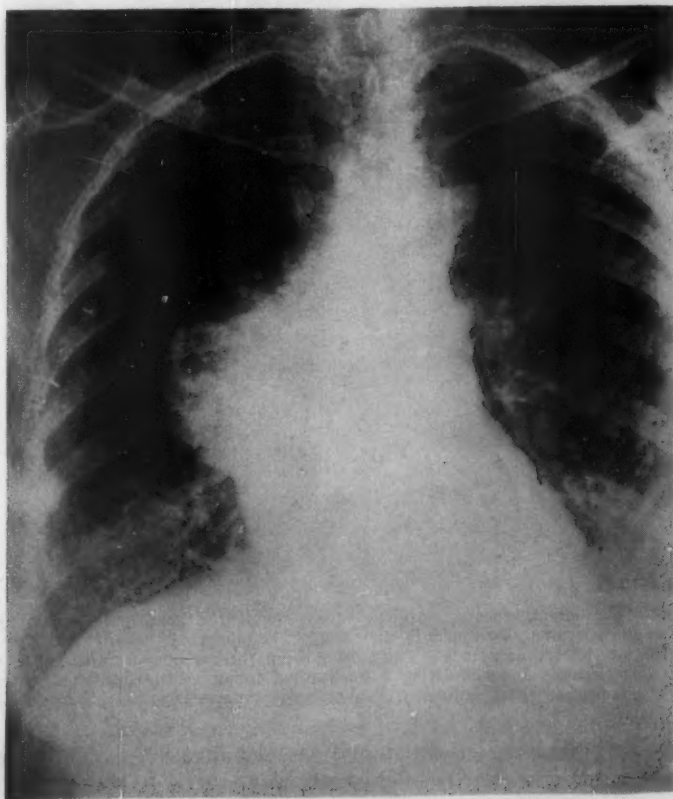


FIG. 22. This is the posterior-anterior chest roentgenogram of a 42 year old male who had dyspnea, chest pain, fever, weight loss, fatigue and anemia. On thoracotomy, this proved to be an undifferentiated carcinoma, presumably bronchogenic. This is an example of an interesting group of tumors, thought by some pathologists to be of different origin than the bronchus.

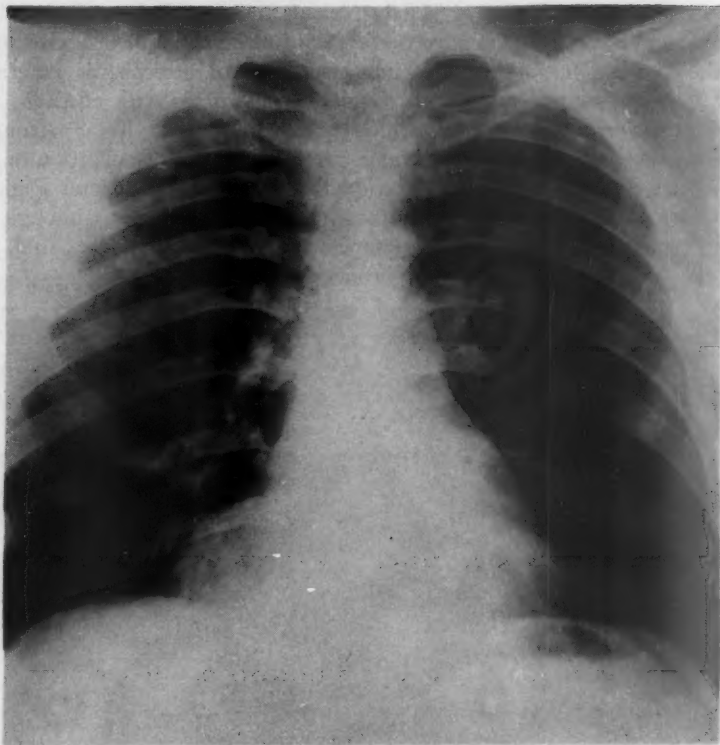


FIG. 23. This 22 year old white male was referred to the hospital because of an abnormality found on his chest roentgenogram. The posterior-anterior chest roentgenogram shows the density to be present in the right cardiophrenic region. No symptoms and no positive findings were present on physical examination.

neck, (2) movement of the mass on swallowing, (3) its configuration on the roentgenogram, and (4) the radioactive iodine uptake over the mass. Although these diagnostic points are not infallible, they are helpful in deciding the operative approach.<sup>32</sup> Removal by a cervical route is the usual procedure. The radioactive iodine uptake may be misleading, especially if the thyroid tissue is nonfunctioning.

*Mediastinal Effusion* (three cases): On occasion, mediastinal pleural effusions will simulate a tumor of the mediastinum. Effusion of this type usually occurs in inflammatory conditions, or from edema fluid due to congestive heart failure.

Usually, mediastinal pleural effusion has no apparent pulsation. This point is important in the differentiation from pericardial effusion, in which the cardiac pulsation is often transmitted. One may note some displacement of the adjacent lung or heart. The roentgenographic findings of

mediastinal pleural effusion are fairly typical, and have been well described by Devic and Savy.<sup>36</sup> There are two types of mediastinal pleural effusions: (1) the *anterior mediastinal* (pseudopericarditis or pericarditis externa), which is most common and which simulates pericarditis with effusion; and (2) the *posterior mediastinal*, which exhibits itself as linear shadows, anterior, and parallel to the vertebral column. A posterior collection on the left will be demonstrated within the cardiac shadow. Sagel and Rigler<sup>37</sup> believe the posterior type to be the most common. At times, although the usual disappearance is due to spontaneous reabsorption of the fluid, the fluid may be emptied by way of the bronchus or esophagus.<sup>38, 39</sup>

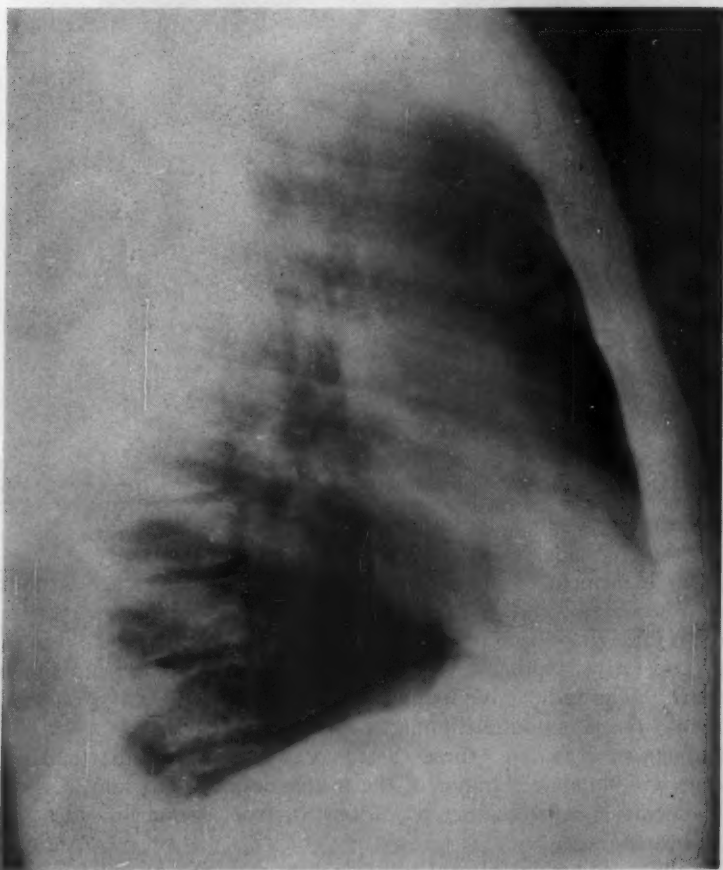


FIG. 24. The right lateral x-ray examination showed the density to be round and to overlie the cardiac shadow. Because the lesion was indeterminate, a thoracotomy was performed and the mass removed. It was a "spring water" type of cyst, and proved to be a pericardial cyst. This is a characteristic history and radiographic appearance for a pericardial cyst. Most are located in the right cardiophrenic area.

All of our examples of this type of mediastinal density cleared spontaneously.

*Aneurysms and Abnormal Vascular Masses* (68 cases): An angiogram is essential for the proper evaluation of a mass which causes suspicion of a vascular abnormality. Angiocardiography can distinguish a vascular from an avascular lesion. In clinics where this procedure is not employed, exploration may be done with a diagnosis of a mediastinal tumor. These operations have been performed in error in cases of right-sided aorta, dilated large left auricle, coarctation of the aorta (poststenotic dilatation), aneurysms of the innominate artery, common carotid artery, ascending transverse and descending aorta, and pulmonary artery.

With the advent of angiocardiography, vascular lesions can be recognized and corrective operations planned. Demonstration of irremediable vascular lesions is also possible.

Angiocardiographic technics demonstrated the true nature of a right mediastinal mass. This tumor reportedly regressed after radiotherapy administered elsewhere. An angiogram demonstrated an idiopathic dilatation of the pulmonary artery. Other instances of referred patients who had had mistaken diagnoses of mediastinal neoplasms instead of vascular abnormalities were encountered.

A report by Deterling<sup>40</sup> shows the need for a thorough study before surgical exploration.

*Lipomas* (two cases): The lipomatous tumors are rare; they may be benign (the more common), or malignant, as a sarcoma. The radiographic appearance of a more radiolucent type of shadow suggests a lipoma. When present, a translucent periphery is a valuable roentgenographic sign.<sup>41, 42</sup> Some have an "hourglass" appearance, representing an intrathoracic and extrathoracic portion. This characteristic may be observed in (1) cervico-mediastinal tumors passing from mediastinum to neck, and (2) transmural, passing through the chest wall, through the intercostal space and, rarely, through the sternum or diaphragm.

The intrathoracic type of lipoma may be asymptomatic, and its discovery depends upon the disclosure of a shadow on the routine chest films. Symptoms present may be due to pressure on mediastinal structures.

The abnormal shadow may be confused with a pericardial effusion or cardiac enlargement. The "hourglass" appearance may lead to suspicion of this tumor.

Only two lipomas were encountered in this series, and one was malignant.

*"Bronchogenic Carcinoma"* (eight cases): Bronchogenic carcinoma often presents as a mediastinal tumor. It is usually associated with symptoms. Dyspnea, weight loss, pain in the chest, hoarseness and vena caval obstruction are most common, but *unfortunately these manifestations are late in appearance.*



FIG. 25. This is the anterior-posterior tomographic study of a large mediastinal mass hidden by the cardiac silhouette, which was found in a 34 year old male who had substernal pain and marked dyspnea, aggravated by exertion.

The tumors referred to are confined to the mediastinum and are usually undifferentiated and anaplastic, without definite evidence of origin from the lung. Many authorities will not classify them as bronchogenic carcinoma. It is therefore believed that a separate tumor, "mediastinal carcinoma," may be represented by this group.<sup>4, 14, 18</sup> Four were found in patients under 40 years of age.

*Pericardial Cysts* (five cases): These congenital defects of the pericardial sac are notable for the radiographic shadows which they cast in an asymptomatic patient. Occasionally, the pericardial cysts become infected, but usually they are benign and harmless. The most common location is at the right anterior cardiophrenic angle; however, in three of our cases the cysts were present along the left heart border. Occasionally they may be multiloculated, and some are attached by a pedicle to the pericardium, so

that they may change location with different body positions. It is not uncommon to see radiographic changes in outline from examination to examination. Pericardial cysts usually come to thoracotomy because it is not possible to distinguish them from the more serious lesions. Communication with the pericardial cavity is usually absent,<sup>3</sup> but we found one case with communication with the pericardial sac.

*Inflammation (278 cases):* When granulomatous inflammatory disease presents as hilar and upper mediastinal enlargement, there is considerable resemblance to lymphoma. In instances of tuberculosis, histoplasmosis and sarcoidosis, where there is a characteristic bilateral hilar and paratracheal lymph node enlargement associated with pulmonary parenchymal involvement, the distinction from other mediastinal lesions is relatively easy. However, an atypical silhouette on the radiologic examination may be confusing. Unilateral hilar enlargement alone can be troublesome. Scalene node biopsy is most helpful, and associated clinical findings may strengthen



FIG. 26. The lateral tomographic study, showing the mass to be filled with spotty calcification. When removed, this was a large tuberculoma which was subcarinal and impinging on both major bronchi.

the diagnosis of granulomatous disease. Scalene node biopsy has established the diagnosis in 72% of the patients with this type of mediastinal disease who did not have other helpful findings. Thoracotomy may be resorted to if none of the other findings is present.

In granulomas due to infection, the presence of fibrosis and calcification may be helpful. There is a definite predilection for involvement of the lymph nodes where the azygous vein joins the superior vena cava.<sup>43</sup> Storey and Lyons<sup>44</sup> and Kunkel<sup>45</sup> reported that tuberculomas usually present as smooth, oval or rounded lobulated masses adjacent to the trachea and protruding into the right thorax. However, other tumors, right-sided aortic arches, neurofibromas and even lymphomas have this appearance. Thoracotomy may be necessary to make the diagnosis, and removal may present difficulties because of the dense inflammatory reactions associated with granulomas. Involvement of fibrous adhesions may result in injury to the phrenic nerve, superior vena cava, trachea and other structures. For this reason, the diagnostic routine must be thorough; if the diagnosis is established, antituberculosis therapy or other indicated therapy should be employed before a thoracotomy is done.

*Rarer Types:* There are other mediastinal tumors which are less common: chylous cysts, myxomas, fibromas, xanthofibromas, chondromas, plasma cell myelomas and meningoceles. None is included in this reported group. Although rare, a hemangioma of the left ventricle was encountered. No instance of parathyroid adenoma was found.

Gastroenteric cysts are rare. They are usually located along the spine in the posterior mediastinum.<sup>24</sup> There were two cases in our series. Intestinal mucosa is found in most, and is often accompanied by peptic ulceration. This tumor is more common among males. The great majority are found in early life (up to four years of age). Slight pain and dyspnea are the clinical symptoms. Occasionally there is bronchial compression. Scoliosis occurs when they become large.

Metastases may produce mediastinal masses, and are reported as most common with pancreatic and gastric carcinomas, but in our experience with a younger population, testicular tumors were the most frequent cause. Diagnosis can be established by history and clinical findings. The scalene node biopsy is most fruitful in this type of problem.

#### DISCUSSION

The mediastinal tumors may be a source of confusion in differential diagnosis. It is axiomatic that only by microscopic examination of the excised specimen, or a portion thereof, can an accurate histologic diagnosis of a mediastinal tumor be made. However, a number of diagnostic procedures are available which may yield valuable information in the study of a mediastinal mass. An orderly investigation, even in the absence of establishing a definite diagnosis, will commonly indicate the proper therapeutic

approach, whether it be surgery, irradiation, drug or chemical therapy, or a further period of observation.

In this brief paper, the various procedures are merely listed (table 2). The roentgenographic examination is far more important and informative than any other. Valuable information is given by radiologic studies, and it is often possible to deduce the probable nature of the lesion on the basis of information obtained from films and fluoroscopy. The establishment of the usual locations and common characteristics of the various tumors and non-neoplastic masses found in the mediastinum is of the greatest assistance to the clinician in the investigation of these lesions in that location. Pre-operative diagnosis is more accurate in tumors with well known radiologic

TABLE 3  
Incidence of Mediastinal Tumors Grouped Under Basic Types

Basic Type	No. of Cases	Total Number of Each Type
<b>Cysts</b>		
Thymic	12	
Bronchogenic	2	
Gastroenterogenous	2	
Pericardial	5	
Lymphangitic	1	22
<b>Hernias, Diverticula, Achaliasias</b>		
<b>Hernias</b>		
Hiatus (esophageal-gastric)	16	
Morgagni	4	
Traumatic	3	
Bochadalek	1	
<b>Diverticula</b>		
Traction	4	
Pharyngeal-esophageal	4	
Achaliasias	10	42
<b>Vascular</b>		
<b>Aneurysms</b>		
Great vessels	26	
Innominate artery	3	
Pulmonary artery	2	
Cardiac	5	36
<b>Anomalies</b>		
Dilated tortuous subclavian artery	20	
Coarctation of aorta	5	
Tortuous aorta	3	
Right-sided aortic arch	2	
Varices (bronchopericardial vessel)	1	
Great vessels (di Guglielmo type)	1	32
<b>Neoplasms</b>		
Cardiac metastases	14	
Hemangioma—left ventricle	1	15

TABLE 3—(Continued)

Basic Type	No. of Cases	Total Number of Each Type
Neoplasm		
Malignant Lymphoma		
Hodgkin's	146	
Lymphosarcoma	40	
Reticulum cell sarcoma	8	
Lymphatic leukemia	5	
Follicular lymphoma	4	203
Teratoma and dermoid	35	
Thymoma	26	
Neurogenic tumors	15	
"Bronchogenic" carcinoma	8	
Mesenchymal tumors	5	
Metastatic growths	34	123
Inflammation		
Boeck's sarcoid	160	
Histoplasmosis	53	
Tuberculoma	48	
Coccidioidomycosis	7	
Infectious mononucleosis	7	
Lymph node hyperplasia	3	278
Miscellaneous		
Goiter	20	
Traumatic hematoma	5	
Mediastinitis	3	
Mediastinal effusion	3	31
Grand Total		782

characteristics, such as the lymphomas, neurogenic tumors and teratodermoids. Even these may present atypical features. The experienced investigator is alert to recognize other lesions which may mimic mediastinal masses in their roentgenographic appearance. The clinical importance of recognition of the type and location of the mediastinal mass is stressed, for it is this information which influences the choice of treatment.

From a practical point of view, the teratodermoids and thymomas are most common among anterior mediastinal masses; granulomas, lymphoblastomas and vascular lesions are most common in the middle mediastinum; neurogenic tumors are the usual occupants of the posterior mediastinum.

Although early surgical exploration will be necessary in some patients, one should not neglect or by-pass such a valuable diagnostic procedure as the scalene node biopsy, which is important diagnostically for those granulomas and lymphomas located in the mediastinum. So fruitful is this method of diagnosis in the absence of other available biopsy material that it is of routine use in the study of a mediastinal mass. The angiocardigraphic study is also important, because it allows recognition of vascular lesions and demonstrates those which cannot be corrected.

The vast majority of mediastinal lesions will require thoracotomy. Because vitally important structures are present in the mediastinum which

may be involved by pressure and other effects of a tumor, thus leading to serious or fatal consequences for the patient, *procrastination will not serve the best interests of the patient*. Thoracotomy is of additional value because it often allows complete excision, a definite histologic diagnosis, and information for prognosis, and it implements the intelligent planning of the subsequent management of the patient.

*Therapeutic radiation for diagnostic purposes is mentioned only to be condemned.*

The total number of each type of mediastinal mass is listed by basic types in table 3. This represents an experience with 782 cases. The greatest number is due to lymphomatous and granulomatous disease.

#### SUMMARY

Mediastinal masses may be neoplastic or non-neoplastic. The neoplasms may be benign or malignant, and are dangerous, especially when undiagnosed. Because of the close contact of vital structures in the mediastinum, threatening complications can occur, and the possibility of malignancy is always present with a mediastinal tumor. Of the entire group of 782 cases, 42% were histologically malignant, and many others were life endangering because of size or position. The mediastinal tumors must be differentiated—and usually can be—with the use of modern diagnostic aids. The scalene node biopsy and angiocardiology are two essential diagnostic procedures, and their use may prevent needless exploratory thoracotomy. Angiocardiology gives information about the feasibility of operation, or, in fact, evidence to contraindicate an operation.

Thoracotomy is mandatory, and should not be delayed when other methods cannot establish the diagnosis. Thoracotomy has a low case fatality rate, offers cure in benign lesions, and gives accurate information on the histologic nature and the gross involvement by the tumor. This permits intelligent management and provides valuable information for prognosis.

#### SUMMARIO IN INTERLINGUA

Massas mediastinal es un problema que es incontrate frequentemente in consequentia del crescente uso de roentgenographia in le examine del thorace. Massas mediastinal es etiam discoperite in multe casos durante un stadio asymptomatic.

In le passato, tal massas esseva simplemente tenite sub observation o tractate per irradiation sin le beneficio de un diagnose specific. Al tempore presente, le tendentia prevalentia es intervenir chirurgicamente a un tempore precoce pro facilitar le ablation o le diagnose de tal lesiones. Iste attitude es plus productive que su precursor, sed le recommendation de effectuar thoracotomia in omne casos ha resultate in le tendentia de omitter certe importante mesuras diagnostic, e le operationes effectuate es a vices innecessari. Varie massas mediastinal, como cystes, tumores, e anormalitates cardiovascular presenta frequentemente simile manifestationes clinic. Il es urgentemente desirabile differentiar tal massas como benigne o maligne o como vascular, e on debe responder al question si le ablation chirurgic

de illos promitte effectuar un cura. Si le appropriate studios es effectuate, certe patientes pote evitar un operation que non es necessari.

Le presente reporto es basate super le experientias colligite in le studio de 782 massas mediastinal. In le majoritate del casos, le patientes in iste serie pertine a plus juvene gruppos de etate. Certe typos de tumores e cystes se distingue per un characteristic e satis constante location compartmental in le mediastino. In le mediastino anterior, massas teratodermoide es le plus commun. Illos es sequite per cystes, thymomas, e tumores thyroide e parathyroide. Le mediastino intermediari es le sito usual de cystes bronchogene e gastroenteric, de lymphomas, e de lesiones metastatic, maligne, e granulomatose. In le mediastino posterior, tumores neurogene es le typo predominante.

Le uso de special methodos roentgenographic e de special technicas diagnostic es determinate per le circumstantias del caso particular. Duo manipulationes, le biopsia de nodo scalen e le angiocardigraphia, ha resolvite certes del problemas con le resultado que operationes prematur o innecessari poteva esser evitate.

In nostre serie, 42% del tumores esseva histologicamente maligne. Alteres impericulava le vita del patientes a causa de lor dimensiones o de lor sito. Es includite in le reporto un lista del major technicas diagnostic e un altere del principal aspectos characteristic del varie typos de massa mediastinal. Es sublineate le importantia de recognoscer le typo de massa e su sito con respecto al election del tractamento. Un certe percentage del casos require thoracotomia pro le diagnose e pro le tractamento. In casos de iste genere, procrastination debe esser evitate. Importante informationes, ab le puncto de vista del prognose e del intelligente modo de tractamento, es providite per le thoracotomia.

#### BIBLIOGRAPHY

1. Blades, B.: Mediastinal tumors; report of cases treated at Army Thoracic Surgery Center in the United States, *Ann. Surg.* **123**: 749-765, 1946.
2. Thompson, J. V.: Mediastinal tumors and cysts, *Internat. Abstr. Surg.* **84**: 195-221, 1947.
3. Schlumberger, H. G.: Tumors of the mediastinum, in *Atlas of tumor pathology*, Section V, Fascicle 18, 1951, Armed Forces Institute of Pathology, Washington, D. C.
4. Nelson, T. G., Shefts, L. M., and Bowers, W. F.: Mediastinal tumors: an analysis of 141 cases, *Dis. of Chest* **32**: 2, 123-153 (Aug.) 1957.
5. Schiff, P., and Warren, B. A.: Scalene node biopsy, *Dis. of Chest* **32**: 198-206 (Aug.) 1957.
6. Daniels, A. C.: A method of biopsy useful in diagnosing certain intrathoracic diseases, *Dis. of Chest* **16**: 360-366, 1949.
7. Storey, C. F., and Reynolds, B. M.: Biopsy techniques in the diagnosis of intrathoracic lesions including lung biopsy, mediastinal biopsy and resection of the deep cervical fat pad and its contained nodes. Report of 12 illustrative cases, *Dis. of Chest* **23**: 357-382 (April) 1953.
8. Shefts, L. M., Terrill, A. A., and Swindell, H.: Scalene node biopsy, *Am. Rev. Tuberc.* **65**: 505, 1953.
9. Steinberg, I., Dotter, D. T., and Andrus, W. de W.: Angiocardigraphy in thoracic surgery, *Surg., Gynec. and Obst.* **90**: 45-59 (Jan.) 1950.
10. Abbott, O. A., Hopkins, W. A., and Leigh, T. F.: The role of angiocardigraphy and venography in mediastinal and paramediastinal lesions, *J. Thoracic Surg.* **18**: 869-989, 1949.
11. Steinberg, I., and Dotter, C. T.: The differentiation of mediastinal tumors and aneurysm value of angiocardigraphy, *Brit. J. Radiol.* **22**: 567-572 (Oct.) 1949.
12. Lyons, H. A.: The use of angiocardigraphy as an aid in the diagnosis of pulmonary disease, *J. A. M. A.* **165**: 1939-1943 (Dec. 14) 1957.

13. Maier, H. C.: Diagnosis and treatment of mediastinal tumors, *S. Clin. North America* **33**: 415, 1953.
14. Peabody, J. W., Sturg, L. H., and River, J. D.: Mediastinal tumors, survey of modern concepts in diagnosis and management, *Arch. Int. Med.* **93**: 875-893, 1954.
15. Bradford, M. L., Malton, H. W., and Grow, J. B.: Mediastinal cysts and tumors, *Surg., Gynec. and Obst.* **85**: 467-491, 1947.
16. Storey, C. F., and Lyons, H. A.: Mediastinal masses: a pamphlet printed for an exhibit at A. M. A. session, 1950, in Atlantic City, 1950, Department of Medicine, U. S. Navy, Washington, D. C.
17. Curreri, A. R., and Gale, J. W.: Mediastinal tumors, *Surg., Gynec. and Obst.* **58**: 797 (June) 1949.
18. Conklin, W. S.: Tumors and cysts of the mediastinum, *Dis. of Chest* **17**: 715-740 (June) 1950.
19. Meyer, O. O.: Treatment of Hodgkin's disease and lymphosarcoma, *J. A. M. A.* **154**: 114-120 (Jan. 9) 1954.
20. Hall, C. A., and Olsen, K. B.: Therapy of malignant lymphoma. I. Study of 116 cases. II. A review, *Am. J. Med.* **20**: 392-411 (Mar.) 1956.
21. Craver, L. F.: Reflections on malignant lymphomas, Janeway Lecture of 1956, *Am. J. Roentgenol.* **76**: 849-858 (Nov.) 1956.
22. Maier, H. C.: Bronchogenic cysts, *Ann. Surg.* **127**: 476, 1948.
23. Lambert, A. V.: Etiology of thin-walled thoracic cysts, *J. Thoracic Surg.* **10**: 1, 1940.
24. Laipply, T. C.: Cysts and cystic tumors of the mediastinum, *Arch. Path.* **39**: 153, 1945.
25. Allison, P. R.: Mediastinal cysts of bronchial origin, *Thorax* **2**: 176, 1947.
26. Sabiston, D. C., Jr., and Scott, H. W., Jr.: Primary neoplasms and cysts of the mediastinum, *Ann. Surg.* **136**: 777, 1952.
27. Dobbs, C. H., Peirce, E. C., II, and Rawson, F. L.: Intrapericardial interatrial teratoma (bronchogenic cyst): report of a case correctly diagnosed and successfully removed, *New England J. Med.* **256**: 541-546, 1957.
28. Keynes, G.: The surgery of the thymus gland, *Brit. J. Surg.* **33**: 201, 1946.
29. Blalock, A.: Tumors of the thymic region and myasthenia gravis, *Am. J. Surg.* **54**: 149, 1951.
30. Morgan, W. L., Jr., and Dudley, H. R.: Malignant thymoma and myasthenia gravis: report of a case and review of the literature, *New England J. Med.* **258**: 625-631, 1955.
31. Crile, G., Jr.: Intrathoracic goitre, *Cleveland Clin. Quart.* **6**: 313, 1939.
32. Lahey, F. H.: Surgical management of intrathoracic goitre, *Surg., Gynec. and Obst.* **53**: 546, 1931.
33. Sweet, R. H.: Intrathoracic goitre located in the posterior mediastinum, *Surg., Gynec. and Obst.* **89**: 57, 1949.
34. von der Lieth, W. C., and Lester, C. W.: Posterior mediastinal goiter, use of combined thoraco-cervical approach for excision, *Am. J. Surg.* **85**: 811-814 (June) 1953.
35. O'Malley, R. D., Parsons, W. B., and Ball, R. P.: Intrathoracic goitre, *Surg., Gynec. and Obst.* **93**: 197-208 (Aug.) 1951.
36. Devic, E., and Savy, P.: Les pleurésies médiastinales, *Rev. de méd., Paris* **30**: 365, 460, 499, 1910.
37. Sagel, J., and Rigler, L. G.: Mediastinal pleural effusion. A roentgenologic study, *Am. J. Roentgenol.* **24**: 225-233 (Sept.) 1930.
38. Belot, J.: Un cas de pleurésie médiastine, *Bull. et mém. Soc. de radiol. méd. de Paris* **6**: 194-196, 1914.
39. Barjou, F.: Les pleurésies enkystées de la région du hile, *J. de radiol. et d'électrol.* **1**: 177-182, 1914.

40. Vaughan, R. H., Deterling, R. A., Jr., and Smith, F. A.: Successful excision of an aortic aneurysm explored as a paraspinal tumor, *New England J. Med.* **253**: 15-17, 1955.
41. Keeley, J. L., and Vana, A. J.: Lipomas of the mediastinum, 1940 to 1955, *Surg., Gynec. and Obst.* **103**: 313-322 (Oct.) 1956.
42. Heuer, G. H.: The thoracic lipomas, *Ann. Surg.* **98**: 801-819, 1933.
43. Samson, P. C., Heaton, L. D., and Dugan, P. J.: Mediastinal tuberculoma, *J. Thoracic Surg.* **19**: 333, 1950.
44. Storey, C. F., and Lyons, H. A.: Tuberculomas of the mediastinum, *Am. Rev. Tuberc.* **64**: 327, 1951.
45. Kunkel, W. M., Jr., Clagett, O. T., and McDonald, J. R.: Mediastinal granulomas, *J. Thoracic Surg.* **27**: 565, 1954.

## FAMILIAL HODGKIN'S DISEASE: ITS SIGNIFICANCE AND IMPLICATIONS \*†

By DENNIS V. RAZIS, M.D.,‡ HENRY D. DIAMOND, M.D., F.A.C.P., and  
LLOYD F. CRAVER, M.D., F.A.C.P., *New York, N. Y.*

### INTRODUCTION

"When you can measure what you are speaking about, and express it in numbers, you know something about it, but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind."—Lord Kelvin

FAMILIAL concentration of any given disease may occur as a mere coincidence. This must be emphasized if one is not to be misled by individual pedigrees with a high incidence of a particular disease. With this in mind, it is apparent that we do not know whether the reported cases of familial Hodgkin's disease in the medical literature signify medical curiosities, or whether they carry weighty environmental and genetic implications.

The evidence from the reported cases, however, is against coincidence. By the law of probability, in a relatively rare disease such as Hodgkin's disease the factor of coincidence is expected to operate less, simply because the incidence in the general population is low. Some of the reported cases of familial Hodgkin's disease are unusually impressive. In others, there is a close approximation of the times of onset of the disease in the affected relatives. In still others, there is close approximation of the ages at onset. Although the age distribution of the disease must be taken into account when evaluating this latter phenomenon (the possibility of two people developing Hodgkin's disease at the age of 35 being greater than at the age of 10), it makes the possibility of coincidence quite small.

Yet these facts, though impressive, are not enough to establish the significance of familial concentration with any degree of certainty. In an effort to examine this problem, we attempted to demonstrate with epidemiologic studies the statistical significance of familial Hodgkin's disease. In the process, more questions and problems arose.

\* Received for publication April 6, 1959.

From the Medical Neoplasia Service of the Department of Medicine, The Memorial Center for Cancer and Allied Diseases, New York, N. Y.; the Lymphoma Section, Division of Clinical Chemotherapy, the Sloan-Kettering Institute for Cancer Research, New York, N. Y.; and the Department of Medicine, Cornell University Medical College, New York, N. Y.

† This study was financed by a grant from the Lloyd F. Craver Fund of the Memorial Center for Cancer and Allied Diseases, New York, N. Y.

‡ Special Fellow in Medical Neoplasia, The Memorial Center for Cancer and Allied Diseases, New York, N. Y.

Requests for reprints should be addressed to Henry D. Diamond, M.D., Memorial Center for Cancer and Allied Diseases, 444 East Sixty-eighth Street, New York 21, N. Y.

## THE LITERATURE IN FAMILIAL CANCER AND LYMPHOMA

Familial concentration in cancer has been observed for many years. Its significance and implications have stirred debate and created theories.<sup>1</sup> The earliest attempts to attack the problem on a statistical scale date back to the beginning of the century.<sup>2</sup> A considerable amount of work has been published in the international literature since then.<sup>2-8, 12</sup> As experience was gained, the epidemiologic methods became more adequate and the analysis of the results more critical and objective. Northern Europeans, especially the Danes, have particularly emphasized the problem, and their contribution is the largest and most systematic.<sup>3</sup>

Chronologically, one of the earliest investigators in the field was Bashford, who in 1908 pioneered a study dealing with the familial occurrence of cancer in general. Today, his data are considered to have been obtained uncritically.<sup>3</sup>

Little in 1923, Waaler in 1931, Wassink in 1935 and Hanhart in 1943 studied the familial occurrence of cancer in Northern European countries. Jacobsen in 1946<sup>4</sup> investigated the familial occurrence of cancer of the breast in Denmark, and expressed the opinion that there was an inherited tendency to develop cancer in this site. Videbaek in 1947<sup>6, 7</sup> published his thesis on *Heredity in Human Leukemia and Its Relation to Cancer*. His study produced statistical evidence of familial concentration in leukemia and an excess of relatives with cancer in the leukemia probands.

Videbaek expressed the opinion that the familial concentration was due to the inheritance of a single gene of low penetrance. Though his study was praised universally as being extremely careful and laborious, several objections and criticisms were raised. His major critic, Busk, demonstrated that when one considered only the immediate relatives, who constitute the only members of importance in statistical studies of this kind, there was no significant concentration of familial leukemia.<sup>9, 10</sup> Furthermore, the theory of one gene of low penetrance was not accepted unequivocally by the geneticists.<sup>11</sup> There were and remain strong objections to Videbaek's theory that leukemia is not an infectious disease, and to his lack of consideration of environmental similarities as a possible cause of familial concentration.

In 1948 Schinz, Cocchi and Neuhaus<sup>2</sup> published their study of familial cancer, sarcoma and Hodgkin's disease. Their control groups were very limited. In 1951 Morgensen<sup>2</sup> investigated the familial occurrence of cancer of the esophagus in Denmark, and concluded that it is doubtful that the familial concentration is strictly genetic. Brobeck in Denmark<sup>8</sup> and Murphy in the United States<sup>8</sup> in 1949 and 1952, respectively, reported their studies in familial cancer of the uterus. Murphy considered cancer of the body as one epidemiologic unit, a concept which has been much criticized.<sup>2</sup> In 1954 Videbaek published his study on *The Etiology of Gastric Cancer*.<sup>12</sup> In this work he seemed more aware of the factor of environment, and projected clearly the problem of heredity versus "false heredity." However,

his conclusions that the predisposition to gastric cancer is inherited and that exogenous factors may accelerate this development were not sufficiently supported. In 1955 Macklin<sup>8</sup> substantiated Videbaek's findings in gastric carcinoma, and recorded similar findings in familial "intestinal cancer."

It is worth while to note that, almost without exception, each of the reported studies of familial cancer and lymphoma has shown a significant familial concentration. One must keep in mind, however, the objections to the sufficiency of the epidemiologic methods in use and to the accuracy of the obtained data.

*The Significance of Twins in Cancer:* Twins are valuable in genetic studies and for testing and formulating the results of epidemiologic studies on the familial occurrence of diseases. In neoplastic diseases, however, this material has only potential value, and so far the study of twins has not produced satisfying generalizations concerning the genetic theory of cancer.

Although cases of concordant and discordant twins with cancer have been reported, these cases are selected, do not represent the twin population, and therefore have little value as a "sample" for generalizations. Valid sampling is made even more difficult by the fact that authors report cases of twins according to their attitude towards concordance and discordance. Some authors apparently feel that concordance is significant and deserves publication, while others preserve the opposite attitude. Earlier investigators<sup>12-16</sup> used the reported cases and their own cases of twins with cancer in their studies. If one is willing to accept this material uncritically, and apparently some workers are,<sup>17-19</sup> it would seem that the influence of heredity on the development of cancer is almost established. Gorer, however, considers the studies of the earlier investigators to be "badly biased."<sup>2</sup>

It must also be kept in mind that chance coincidence may operate in twins, as in anything: "In the Confederate Museum at Richmond, Va., there is a photograph of L. T. and J. H. Walker, twin Confederate soldiers, sitting side by side, each having lost his left leg as the result of battle wounds."<sup>14</sup>

Danish and German workers who have undertaken systematic studies of cancer in twins have reached no conclusions.<sup>2</sup> Their authoritative opinions are that twins must have been observed for decades before one would be able to say that the degree of concordance is greater than would be expected for patients observed over the same period.

In Hodgkin's disease there are two cases of concordant twins<sup>20, 21</sup> and five cases of discordant twins<sup>22-25</sup> reported in the literature, along with an unknown number of unpublished cases. Peacocke's case of concordant twins is diagnostically unconvincing, and thus of little value. Remde reported the second case of concordant identical twins in 1950.<sup>21</sup>

If Hodgkin's disease is concentrated in certain families, an excess of concordant pairs with both monozygotic and dizygotic twins should be expected. A greater excess for the monozygotic twins would indicate that the familial concentration is mainly genetic. However, Hodgkin's disease is a relatively

rare condition, and involves few cases of twins. It would seem highly improbable, therefore, that any question of the genetic origin of the disease could be solved by studying twins alone.

#### THE LITERATURE IN FAMILIAL HODGKIN'S DISEASE

There are 63 instances of familial Hodgkin's disease reported in the international literature,<sup>20, 21, 24-61</sup> with the earliest reports dating back to the end of the 19th Century. A number of the published cases are well documented and confirmed histopathologically. Exceptionally impressive cases have been published of familial Hodgkin's disease in twins, both concordant and discordant,<sup>20-25</sup> in husbands and wives,<sup>38, 50</sup> and in infants and mothers.<sup>25, 45, 53, 62-64</sup>

Not all the reported cases, however, can be considered as incontrovertible. In some there is no reliable histopathologic diagnosis; in others, the genealogic information is not sufficient. Especially doubtful are the earliest reports of familial Hodgkin's disease, due to the lack of reliable histopathologic diagnoses. An example is Peacocke's well known case of Hodgkin's disease in twins.<sup>20</sup> In other cases reported as "familial Hodgkin's disease," the proband had Hodgkin's disease but the relative had another form of lymphoma.

Collection and review of the reported cases have been attempted by different workers, but so far the problem has not been attacked on a statistical scale. Furthermore, it is apparent that the reported cases are selective and do not represent the "universe" of the Hodgkin's population, and that any attempt to use them as a "sample" for generalization would therefore be unjustified.

Hoster and Dratman<sup>25</sup> in 1948 collected 20 reports of familial Hodgkin's disease and clearly formulated their significance:

"... In contrast with these reports are large series of cases occurring in only one member of each family. One member of pairs of homologous twins has been reported to have Hodgkin's disease in five instances, the other member remaining unaffected. Numerous pregnancies in women with Hodgkin's disease have not resulted in diseased offspring except in the rare instances cited. It is difficult to evaluate the significance of the conflicting reports available. Although the assembled evidence suggests a familial incidence, there is no information to indicate whether this evidence, if established, is on the basis of genetic or environmental influence."

Mazar and Straus in 1951<sup>50</sup> reported the second case of marital Hodgkin's disease, and reviewed 33 cases from the international literature. They expressed the opinion that marital Hodgkin's disease is probably a curiosity, but familial concentration in blood relatives may be of significance. They also suggested that Hodgkin's disease is a neoplastic disease initiated by a virus, and that the familial occurrence is similar to Gross' "Vertical Epidemia" in mice, and analogous to the "milk factor of Bittner."

Videbaek in 1955<sup>58</sup> reported a case of familial Hodgkin's disease and stressed the need for statistical evaluation of the problem. He stated that

it is reasonable to assume that Hodgkin's disease is due to a virus infection, since the peak age distribution of the disease "... is far lower than for any accepted cancer."

Actually, this is not true. Embryonal and mixed tissue tumors, and cancer of the testes, kidneys, adrenals and bones, reach their peak of incidence at an earlier age than does Hodgkin's disease. Cancer epidemiologists express the opinion that where there is a shift to the left in the age distribution in cancer, it is suggestive of exogenous and mainly occupational influences.<sup>65</sup>

DeVore and Doan in a recent publication<sup>38</sup> reported the results of a study of the charts of 400 patients with Hodgkin's disease at the Ohio State University Health Center, and 40 patients at the University of Oklahoma Medical Center. Their study produced 16 families, on whom the records were felt to be accurate enough, with two or more members with Hodgkin's disease or with Hodgkin's granuloma in one relative and a different type of lymphoma in another. In six other families, the familial occurrence of lymphoma was "... not considered as sufficiently proved." They concluded that the evidence available from the literature and their own cases indicated "... a definite familial tendency favorable to the development of lymphomas ..." and that "... our incidence of lymphoma found in more than one member of the same family is greater than would be accounted for on the basis of chance alone."<sup>38</sup> It is quite doubtful that it is correct to consider as a familial occurrence the development of any lymphoma in the relatives of Hodgkin's disease patients. Furthermore, their conclusion that the familial occurrence is greater than chance coincidence can be drawn only from statistical studies, and these were not done.

Jackson and Parker reported one family in which four immediate members were affected.<sup>43</sup>

In contrast to the aforementioned studies, two authors have reported no familial cases in two groups of Hodgkin's disease patients, 54 and 212 cases, respectively.<sup>66, 67</sup>

Although the reported cases in the international literature are not suitable for statistical survey, they could give valuable information if they were documented sufficiently. Similarities in age at onset, time of onset, and common environment could give indications of hereditary and environmental factors and their relative significance. Very few of the reports give enough data from which to elaborate hypotheses and conclusions, although in some of these communications there are striking similarities in the environment, time of onset and, more rarely, age at onset.<sup>25, 32, 44, 45, 49, 53, 57, 62, 63</sup> One might draw the cautious conclusion that in the reported familial cases there is little evidence of hereditary predisposition in Hodgkin's disease.

#### METHODOLOGY

The objective of our epidemiologic study of familial Hodgkin's disease was to draw a generalization from a "sample." The generalization to be

applied in the "universe" (the general Hodgkin's disease population) is either that familial concentration of the disease is significant or that it is a random phenomenon. The "sample" from which we attempted to derive the generalization is the Hodgkin's disease population of Memorial Center.

It is well recognized that by using this methodology we are confronted with an unknown factor—representativeness of the "sample" in relation to the studied character. It is possible to find the familial occurrence of Hodgkin's disease in the "sample" with a reasonable degree of accuracy. Whether this familial occurrence reflects the real incidence in the "universe" (which is unknown) remains a debatable question. Nevertheless, in this study of Hodgkin's disease, as in any similar study, this method remains the only practical one. The alternative, the study of familial occurrence in the "universe," is quite impractical.

Ideally, of course, the "sample" should have the same known "characteristics" as the "universe" in order to support soundly the generalization about the unknown character.

The "sample" used in this study is of sufficient size and is definable. All of the study group cases have had a histopathologic diagnosis made by members of the Department of Pathology of Memorial Center. This provides a high diagnostic accuracy in the studied group, and thus the validity of the results is soundly supported.

In the present study, four control groups were used: (1) the lymphosarcoma group, (2) the leukemia group, (3) the malignant tumor group, and (4) the benign disease group.

The choice of control groups in this study was made in the hope that possibly we could not only answer the question of the meaning of familial concentration in Hodgkin's disease, but also find a hint as to relationships among the different lymphomas. Ideally, control groups in this type of study should be similar to the study group in all characters except the one under study. As this is never the case, the use of control groups remains a weak and vulnerable point. One has to remember, however, that, generally, the epidemiologic methods in use are far from ideal and often barely adequate.

The case histories of the study and control groups were studied mainly for a family history of lymphomas in the immediate relatives (those of first degree relationship, i.e., parents, siblings and children). The occurrence of lymphomas in distant blood relatives and nonblood relatives is listed, but this information is not used in the statistical analysis of the data. Only immediate relatives are used for statistical purposes. This is done because patients having the disease are naturally aware of other members of their family, however distant, who also had the disease. This is not true for the corresponding control individuals who, having no interest in the disease, do not seek out such information. Therefore, if information concerning distant relatives was used, this difference would be a source of bias. As

far as immediate relatives are concerned, both the patients with the disease and the control individuals are usually equally well—or badly—informed.<sup>68</sup>

As mentioned previously, the cases were studied not only for familial occurrence of Hodgkin's disease but for familial occurrence of lymphosarcoma and leukemia as well. Where a positive family history of Hodgkin's disease or lymphosarcoma was given, an effort was made to locate a summary of the case, and to locate and submit the pathology slides for review in the Department of Pathology of Memorial Center. The same effort was made in all of the groups, including the study and comparison groups. No attempt was made to verify the diagnosis in familial leukemia. Family histories of tuberculosis and diabetes mellitus were also listed in each of the three lymphoma groups, while family histories of pernicious anemia were listed in the Hodgkin's disease and leukemia groups only.

The entire survey, including study and control groups, involved 4,027 patients.

TABLE 1  
Hodgkin's Disease Group: Age Distribution by Apparent Onset of Disease

	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+	Total
Males	9	74	167	157	97	81	44	14	643
Females	3	61	166	101	56	42	25	5	459
Total									1,102

#### THE STUDY GROUP

The study group was composed of 1,102 patients with Hodgkin's disease who had been seen at Memorial Center from 1918 up to the beginning of 1958. They were seen either as in-patients or out-patients in the clinic, or as private patients of two of us (L. F. C. and H. D. D.).

An unequivocal histopathologic diagnosis was a *sine qua non* for inclusion of the case in the study. Many more patients with Hodgkin's disease have been seen at Memorial Center during these years, but either the histopathologic diagnosis was unconfirmed or the case history could not be located.

*Age and Sex Distribution:* The age and sex distribution of the study group at the time of the Memorial Center admission is given in figure 1. The age distribution as determined by apparent onset of the disease is given in table 1. As expected, there is, in the latter, a slight shift to the left in favor of the groups 10 to 19 and 20 to 29, the group zero to nine being unchanged, and the groups from 30 to 39 to 70 plus being slightly decreased. The age and sex distribution in the study group is compared with the group from Denmark,<sup>10</sup> composed of 864 patients (figure 2); the group from Connecticut,<sup>69</sup> composed of 434 patients (figure 3); and the group from Brooklyn,<sup>70</sup> composed of 546 patients (figure 4).

There are controversial reports in the literature about the age and sex distribution in Hodgkin's disease.<sup>25, 43, 59, 70-77</sup> When figures 1 through 4 are compared it seems clear that there is a shift to the left in the Memorial Center group, as was expected. The reasons for this are not known, but it is recognized that age distribution in a hospital population favors a shift to the younger age groups.

*The Racial Composition:* The racial composition of the study group is given in table 2. In the same table, the racial composition of the 1957

AGE DISTRIBUTION 1102 CASES OF HODGKIN'S DISEASE

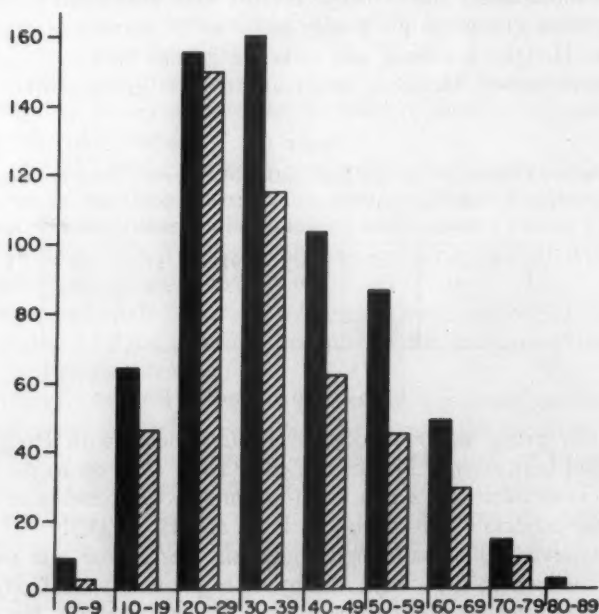


FIG. 1. Age distribution in the study group at the time of the first Memorial Center admission. Solid columns represent male patients. Shaded columns represent female patients.

Memorial Center admissions is listed. All of the Orientals in the study group are Chinese. Although no sound conclusions about the racial distribution in Hodgkin's disease can be drawn from these data, the comparison of the two groups is in favor of previous statements<sup>25, 67, 70, 74</sup> that Hodgkin's disease is rarer in the Japanese and in Negroes. The evidence, however, is far from established.

*The Histopathologic Diagnoses:* The histopathologic diagnoses in the study group are listed according to age group in table 3. In 527 cases, the

AGE DISTRIBUTION OF HODGKIN'S DISEASE  
IN DENMARK 1943-1952

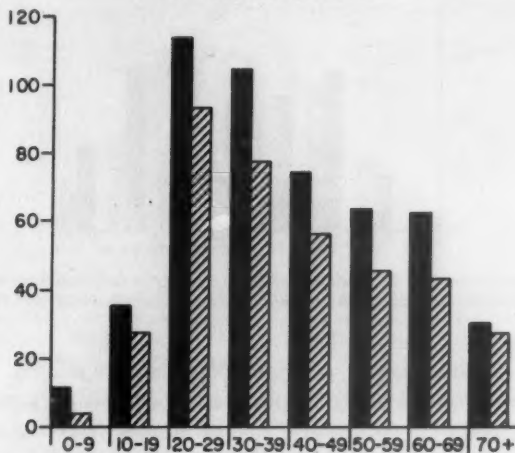


FIG. 2. Age distribution of Hodgkin's disease patients in Denmark during the years 1943-1952. Solid columns represent male patients. Shaded columns represent female patients.

diagnosis was Hodgkin's granuloma; in 399 cases, Hodgkin's disease, not further classified; in 62 cases, Hodgkin's sarcoma; in 57 cases, Hodgkin's paragranuloma. In another 57 cases, different types of Hodgkin's disease were coexisting, or the disease had apparently changed from one form to another (quite often Hodgkin's granuloma terminating as Hodgkin's sarcoma). In a few of these cases, Hodgkin's disease coexisted with another variety of lymphoma.

Interestingly enough, in one case a patient with Hodgkin's disease,

AGE DISTRIBUTION OF HODGKIN'S DISEASE  
IN CONNECTICUT 1935-1946

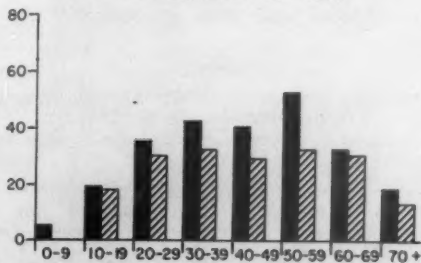


FIG. 3. Age distribution of Hodgkin's disease patients in Connecticut during the years 1935-1946. Solid columns represent male patients. Shaded columns represent female patients.

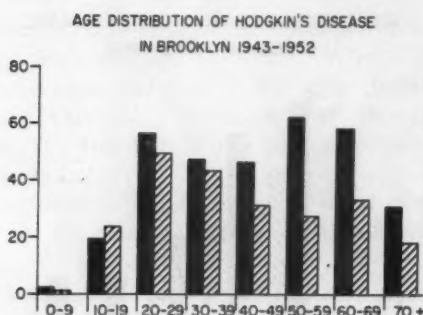


FIG. 4. Age distribution of Hodgkin's disease patients in Brooklyn during the years 1943-1952. Solid columns represent male patients. Shaded columns represent female patients.

Class I,\* had a node biopsy of Hodgkin's paraganuloma. Years later another node developed, and the biopsy was Hodgkin's paraganuloma.

Despite the previous statement, "... in no case have we seen a patient with primary Hodgkin's sarcoma—that is, not preceded by Hodgkin's granuloma—under twenty years of age . . . ,"<sup>48</sup> "primary" Hodgkin's sarcoma was found in five instances in the 10 to 19 age group.

*Postmortem:* An autopsy was performed in 234 patients out of 1,102 (21.2%). In four instances, although the diagnosis of Hodgkin's disease had been previously established by node biopsy, no evidence of this disease was found at postmortem. All four patients died from other causes.

*Survival:* The survival of patients with Hodgkin's disease was not a part of this study. We mention only two interesting cases. In one, the diagnosis at the onset of the disease was Hodgkin's sarcoma, and the patient was alive and well 20 years later. In the other case, the disease developed in 1911,<sup>78</sup> and was later diagnosed at Memorial Center as Hodgkin's paraganuloma. The patient died 33 years later, and the postmortem showed Hodgkin's sarcoma.

Several studies from Memorial Center and other institutions on the survival in Hodgkin's disease have been reported.<sup>76, 79-82</sup>

TABLE 2  
Racial Composition of the Study Group as Compared to Memorial  
Center Admissions During 1957

	White		Negro		Oriental		Total
	No.	Per Cent	No.	Per Cent	No.	Per Cent	
Study group	1,081	98.1	14	1.3	7	0.6	1,102
1957 admissions	6,708	97.5	149	2.2	25	0.3	6,882

\* According to Craver's classification, Class I is unicentric disease without constitutional symptoms or other evidences of dissemination.

TABLE 3

The Histopathologic Diagnoses\* in the Study Group According to Age Distribution

Age Group	Hodgkin's Granuloma	Hodgkin's Disease Unclassified	Hodgkin's Paragranuloma	Hodgkin's Sarcoma	Others†	Total
0-9	8	2	2	0	0	12
10-19	63	31	4	5	7	110
20-29	152	113	11	17	12	305
30-39	124	97	14	16	24	275
40-49	80	62	11	8	4	165
50-59	61	54	5	7	4	131
60-69	32	32	5	5	4	78
70+	7	8	5	4	2	26
Total	527	399	57	62	57	1,102

\* All verified by pathologists of the Department of Pathology at Memorial Center.

† Patients in whom different types of Hodgkin's disease were coexisting, in whom the disease had apparently changed from one form to another, and in whom Hodgkin's disease existed with another variety of lymphoma.

*Suicide:* Two patients out of the total of 1,102 committed suicide. This was also the case in the lymphosarcoma group (two patients out of 1,269).<sup>88</sup>

*The Occurrence of Hodgkin's Disease, Lymphosarcoma and Leukemia in the Relatives of Probands with Hodgkin's Disease:* The familial cases of Hodgkin's disease are divided into "proved" and "not proved" cases. In the "proved" cases, the histopathology of both proband and relative was verified at Memorial Center. In the "not proved" cases, the histopathology of the proband but not of the relative was verified at Memorial Center. In our cases of familial Hodgkin's disease, where both relatives were Memorial

TABLE 4

## Familial Hodgkin's Disease—Immediate Family

## I. "Proved" Cases in Probands and Relatives

Family	Proband*	Relative
1	W. R., 35, m/w	2 sisters
2	J. M., 39, f/w	Son
3	A. D., 30, m/w	Brother
4	A. M., 19, m/w	Mother
5	L. S., 38, f/w	Father
6	B. P., 38, f/w	Mother
7	M. K., 24, m/w	Brother
8	R. H., 25, m/w	Sister
9	H. S., 53, m/w	Son
10	S. S., 41, f/w	Son
11	M. S., 47, f/w	Daughter
12	P. M., 52, m/w	Sister
13	P. P., 53, m/w	Daughter

## II. "Proved" Cases in Probands but not in Relatives

Family	Proband	Relative
14	C. B., 31, m/w	Brother
15	A. L., 50, f/w	Father
16	S. K., 32, f/w	Brother
17	J. W., 18, m/w	Twin brother (fraternal)
18	N. B., 18, f/w	Mother

\* The digits refer to the age of the proband; m/w = male/white; f/w = female/white.

Center patients, the term "proband" is given to the relative first admitted to Memorial Center.

The familial cases were studied for similarities in the age at onset, time of onset, environment, and anatomic location of the disease at the beginning of the illness. The available information is given in the addendum.

Hodgkin's disease affected immediate relatives in 18 cases, 13 "proved" and five "not proved" (table 4). Brief summaries are given in the addendum (families 1 through 18).

Hodgkin's disease affected distant relatives in 11 cases, three "proved" and eight "not proved." The occurrence of Hodgkin's disease in distant

TABLE 5  
Incidence of Lymphosarcoma in the Immediate Families of the  
Study and Control Group Patients

Family	Proband	Relative	Verification of Diagnosis in Relatives
A. Hodgkin's Disease Group			
31	60-69, f/w	Son—LSA	Proved
32	10-19, f/w	Mother—RCS	Proved
33	50-59, m/w	Mother—LSA	Proved
34	20-29, f/w	Brother—LSA	Not proved
B. Lymphosarcoma Group			
42	40-49, m/w	Brother—LSA	Not proved
43	50-59, f/w	Daughter—LSA	Not proved
44	30-39, f/w	Brother—LSA	Not proved

(There were no cases of lymphosarcoma in the relatives of patients in the Leukemia, Benign Disease, and Malignant Tumor Control Groups.)

Key:

LSA—lymphosarcoma  
RCS—reticulum cell sarcoma  
m/w—male/white  
f/w—female/white

relatives of the probands, though reported (families 6, 19 through 28 in the addendum), is not included in the statistical analysis of the data.

Three pairs of twins, one with both members affected with Hodgkin's disease and two with one member affected, are included in this study. The cases are reported in the addendum (families 17, 29 and 30). We have discussed previously the significance of twins in cancer in general and in Hodgkin's disease in particular. From the few cases included in this study, we can offer no contribution to the unsettled problem of twins in neoplastic diseases.

In four instances, three "proved" and one "not proved," immediate relatives of probands with Hodgkin's disease developed lymphosarcoma (families 31, 32, 33 and 34 in the addendum). They are also listed in table 5.

TABLE 6  
Incidence of Leukemia in the Immediate Family of the  
Study and Control Group Patients

Proband	Relative	Diagnosis
A. Hodgkin's Disease Group		
1. 40-49, m/w*	Father	Acute leukemia
2. 20-29, f/w†	Brother	Leukemia
3. 30-39, m/w	Father	Leukemia
4. 30-39, f/w	Father	Leukemia
5. 30-39, f/w	Father	Leukemia
6. 50-59, m/w	Father	Leukemia
7. 30-39, f/w	Brother	Leukemia
8. 20-29, m/w	Mother	Leukemia
9. 60-69, m/w	Father	Chronic lymphatic leukemia
10. 20-29, f/w	Brother	Chronic lymphatic leukemia
11. 20-29, m/w	Mother	Chronic lymphatic leukemia
12. 50-59, m/w	Brother	Leukemia
B. Lymphosarcoma Group		
1. 50-59, f/w	Daughter	Leukemia
2. 40-49, f/w	Sister	Leukemia
3. 50-59, f/w	"Child"	Leukemia
4. 10-19, m/w	Brother	Acute leukemia
C. Leukemia Group		
1. 40-49, f/w	Sister	Leukemia
2. 40-49, m/w	Mother	Chronic lymphatic leukemia
3. 40-49, m/w	Father	Chronic myelogenous leukemia
D. Malignant Tumor Group		
1. 60-69, m/w	Sister	Leukemia
2. 60-69, m/w	Sister	Leukemia
3. 50-59, f/w	Sister	Leukemia
4. 40-49, f/w	Father	Leukemia
E. Benign Disease Group		
1. 40-49, f/w	Mother	Leukemia
2. 20-29, f/w	Mother	Leukemia
3. 20-29, f/w	Father	Plasma cell leukemia
4. 20-29, f/w	Mother	Leukemia
5. 10-19, f/w	Sister	Leukemia
6. 60-69, f/w	Sister	Leukemia
7. 50-59, f/w	Mother	Leukemia
8. 50-59, f/w	Son	Leukemia

\* Male/white.

† Female/white.

In 12 cases, immediate relatives of probands with Hodgkin's disease are reported as having had leukemia. They are listed in table 6. Several other known cases of leukemia in distant relatives are not listed in this study.

*The Occurrence of Tuberculosis, Diabetes Mellitus and Pernicious Anemia in the Relatives of Probands with Hodgkin's Disease:* Forty-one probands with Hodgkin's disease had 47 immediate relatives with tuberculosis. In 35 probands, only one relative was involved (12 fathers, six mothers, nine brothers, seven sisters and one son). In six probands, more than one immediate relative was affected (two cases of mother and father, two cases of sister and sister, one case of father and brother, and one case of brother and sister).

In only one instance did the proband also have active tuberculosis.

Fifty-six probands with Hodgkin's disease had 60 immediate relatives with diabetes mellitus. In 54 of these cases, only one relative was reported as diabetic (16 fathers, 26 mothers, five sisters and seven brothers). In two probands, more than one member was diabetic (one case of father, sister and two brothers, and one case of father and mother).

Seven probands out of the 56 also had diabetes.

TABLE 7  
Lymphosarcoma Control Group: Age Distribution by  
Apparent Onset of Disease

	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+	Total
Males	28	41	66	124	164	174	144	51	792
Females	13	17	29	70	97	116	95	40	477
Total									1,269

In three instances, immediate relatives (two mothers and one brother) and in one instance a distant relative (grandfather) reportedly had pernicious anemia. Cases of pernicious anemia in immediate and distant relatives were also found in the leukemia group, but not in the other control groups. (In the lymphosarcoma group, however, this information was not available.)<sup>8a</sup>

The frequency of occurrence of pernicious anemia in the relatives of patients with leukemia has been noticed in the literature. A genetic relationship between the two diseases has been suggested.<sup>7</sup> However, there is no report in the literature about the occurrence of pernicious anemia in the relatives of Hodgkin's disease patients. From our study it would seem that the occurrence of pernicious anemia in relatives of Hodgkin's disease patients is almost as common as in the leukemia relatives.

#### THE LYMPHOSARCOMA CONTROL GROUP

The lymphosarcoma control group consists of 1,269 patients with lymphosarcoma from Memorial Center. The data were available from a

study recently completed by Rosenberg, Diamond and Craver.<sup>83</sup> In figure 5 the age and sex distribution of the lymphosarcoma group is listed according to the first Memorial Center admission. In table 7 the age and sex distribution is listed according to the apparent onset of the disease. As in the Hodgkin's disease group, all of the cases had pathologic proof at Memorial Center. The information available to us from the case histories in this group was family history of Hodgkin's disease, lymphosarcoma and leukemia.

*Occurrence of Hodgkin's Disease, Lymphosarcoma and Leukemia in the Relatives of Probands with Lymphosarcoma:* In four instances, two "proved" and two "not proved," immediate relatives of lymphosarcoma pro-

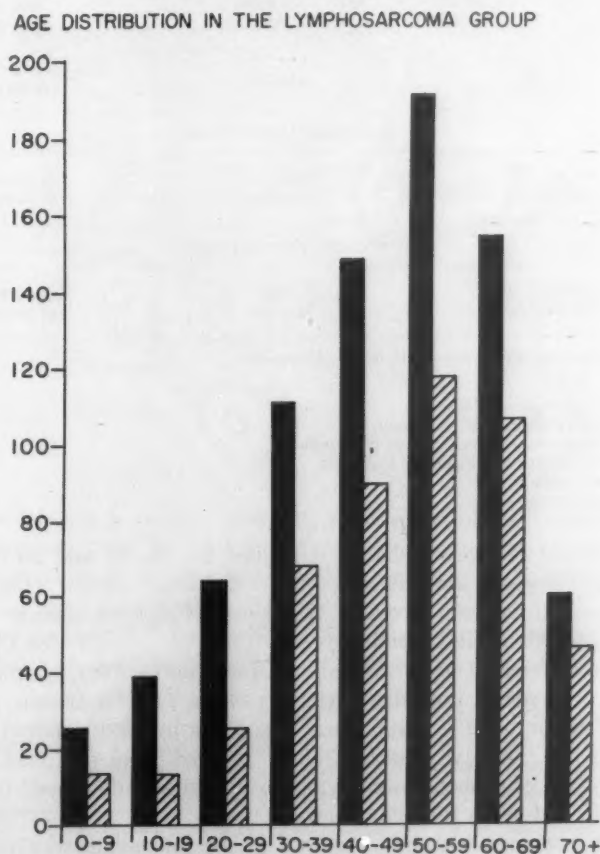


FIG. 5. Age distribution in the lymphosarcoma control group at the time of the first Memorial Center admission. Solid columns represent male patients. Shaded columns represent female patients.

TABLE 8  
Incidence of Hodgkin's Disease in the Immediate Families  
of the Control Group Patients

Family*	Proband	Relative	Verification of Diagnosis in Relatives
A. Lymphosarcoma Group			
35	40-49, m/w, LSA	Mother	Proved
36	60-69, m/w, RCS	Brother	Proved
37	50-59, m/w, LSA	Brother (and sister?)	Not proved
38	30-39, f/w, LSA	Sister	Not proved
B. Leukemia Group			
47	70-79, f/w, CML	Father	Not proved
48	60-69, m/w, AML	Brother	Not proved
Proband		Relative	Verification of Diagnosis in Relatives
C. Malignant Tumor Group			
1. 40-49, f/w		Sister	Not proved
2. 50-59, f/w		Brother	Not proved
D. Benign Disease Group			
1. 40-49, f/w		Father	Not proved
2. 30-39, f/w		Mother	Not proved

\* These families are summarized in the addendum.

Key:

LSA—lymphosarcoma  
RCS—reticulum cell sarcoma  
CML—chronic myelogenous leukemia  
AML—acute myelogenous leukemia  
m/w—male/white  
f/w—female/white

bands developed Hodgkin's disease (families 35, 36, 37 and 38 in the addendum). They are also listed in table 8. Four distant relatives, one "proved" and three "not proved," developed Hodgkin's disease (families 38, 39, 40 and 41 in the addendum).

In three instances (none "proved" at Memorial Center), lymphosarcoma reportedly occurred in immediate relatives of the lymphosarcoma probands. They are listed in table 5. Summaries are given in the addendum (families 42, 43 and 44). In two instances, one "proved" and one "not proved," distant relatives of probands with lymphosarcoma also developed the disease (families 45 and 46 in the addendum).

In four instances, leukemia occurred in the immediate relatives of probands with lymphosarcoma. They are listed in table 6. In four instances, distant relatives of probands with lymphosarcoma developed leukemia

TABLE 9

### Diagnoses in the Leukemia Control Group

Acute leukemia	19
Acute myelogenous leukemia	61
Acute lymphatic leukemia	23
Acute monocytic leukemia	1
Subacute myelogenous leukemia	2
Chronic myelogenous leukemia	48
Chronic lymphatic leukemia	49
"Leukemia"—type not stated	17
Total	220

(maternal grandmother, maternal grandfather, maternal aunt and second cousin).

## THE LEUKEMIA CONTROL GROUP

The leukemia control group is composed of 220 patients from Memorial Center. Seventeen of these 220 cases were taken from the files of the Department of Epidemiology of Memorial Center, and the remaining 203

TABLE 10

### Types of Leukemia According to Age Distribution

	Acute Leukemia	Acute Myelo- genous Leukemia	Acute Lymphatic Leukemia	Acute Monocytic Leukemia	Subacute Myelo- genous Leukemia	Chronic Myelo- genous Leukemia	Chronic Lymphatic Leukemia	"Leu- kemia"
0-9	15	28	17					
10-19	3	7			1	3		
20-29		8	1		1	3		
30-39		3		1		7	1	2
40-49		8	3			13	8	4
50-59	1	1	1			12	18	5
60-69		6	1			6	20	6
70+						4	2	
Total	19	61	23	1	2	48	49	17 220

cases were selected at random from the inactive files of the Memorial Center Medical Records Library. All have an unequivocal diagnosis of leukemia.

An analysis of the type of leukemia is given in table 9, and the type of leukemia by age group in table 10.

The age and sex distribution of the leukemia group at the first Memorial Center admission is given in figure 6. The age and sex distribution at the

TABLE 11

## Leukemia Control Group: Age Distribution by Apparent Onset of Disease

[illegible]

## AGE DISTRIBUTION IN THE LEUKEMIA GROUP

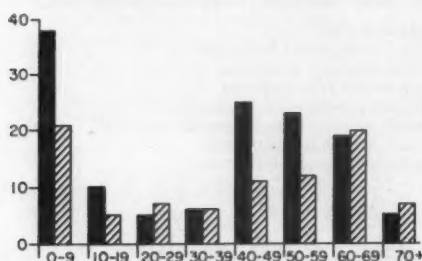


FIG. 6. Age distribution in the leukemia control group at the time of the first Memorial Center admission. Solid columns represent male patients. Shaded columns represent female patients.

time of the apparent onset of the disease is given in table 11. In figure 7 the age and sex distribution of the leukemia group from Connecticut<sup>69</sup> is given for comparison.

In figure 8 the age distribution of the three Memorial Center groups (Hodgkin's disease, lymphosarcoma and leukemia) is given by age group and by percentage of the total in each age group for comparison of the different age distributions in the three groups.

As in the other groups, interesting items were revealed in looking through the cases. In one case in the leukemia group, leukemia developed during pregnancy, and in two cases, leukemia developed shortly (one to two months) after delivery. The infants were normal in all three cases.

In still another instance, the fraternal twin of a patient with leukemia was living and well at the time of this study.

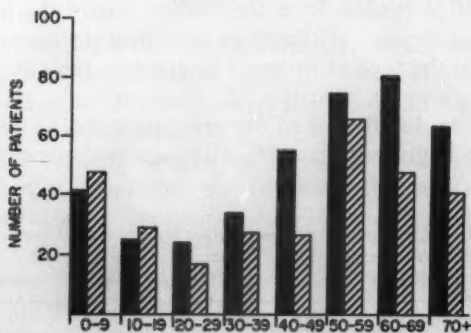
AGE DISTRIBUTION OF LEUKEMIA  
IN CONNECTICUT 1935-1946

FIG. 7. Age distribution of leukemia patients in Connecticut during the years 1935-1946. Solid columns represent male patients. Shaded columns represent female patients.

*Occurrence of Hodgkin's Disease, Lymphosarcoma and Leukemia in the Relatives of Probands with Leukemia:* In two instances, immediate relatives of probands with leukemia were reported as having had Hodgkin's disease. They are listed in table 8. None of the cases was "proved" at Memorial Center. Summaries are given in the addendum (families 47 and 48). There was one "proved" case in the distant family (No. 49 in the addendum).

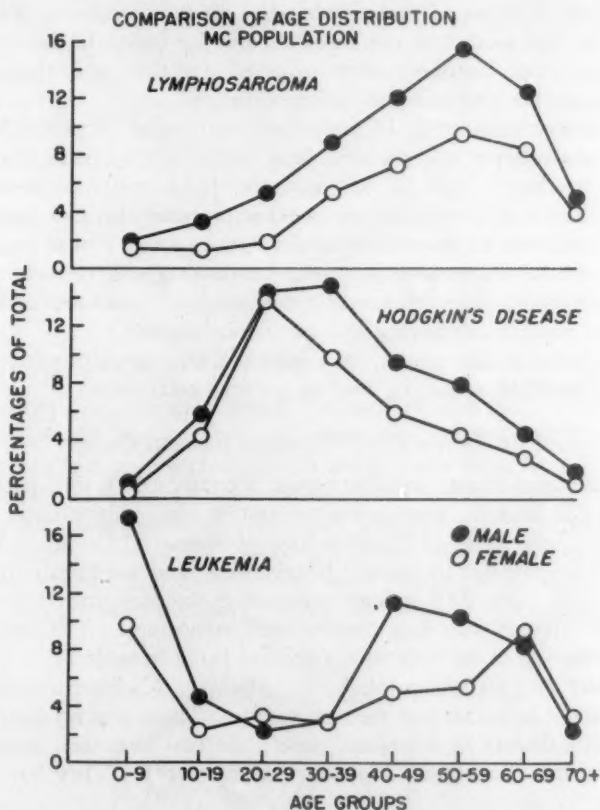


FIG. 8. Comparison of the age distribution in the three Memorial Center groups (Hodgkin's disease, lymphosarcoma and leukemia). The distribution is shown according to the percentages occurring in each decade.

In Videbaek's study of familial leukemia,<sup>7</sup> "... the brother of a leukemia proband (pedigree No. 58) had Hodgkin's disease, and the same was the case with the father of one of the control group."

No case of lymphosarcoma was reported in the immediate or distant relatives of the leukemia group.

Leukemia was reported in the immediate relatives of probands with leukemia in three instances. They are listed in table 6.

In six instances, leukemia was reported in the distant family (maternal uncle, maternal cousin, paternal first cousin, two paternal cousins and one paternal grand uncle).

*Occurrence of Tuberculosis, Diabetes Mellitus and Pernicious Anemia in the Relatives of Probands with Leukemia:* Tuberculosis was reported in six immediate relatives of three probands. In two instances, one member was affected (the mother in one instance, and the father in the other). In one instance, four members were involved (mother and three sisters). In one instance the proband also had tuberculosis.

Diabetes was reported in 16 immediate relatives of 14 probands. In 13 instances, one relative was diabetic (one father, six mothers, three sisters and three brothers), and in one instance, three relatives were diabetic (mother and two sisters). In one case the proband also had diabetes.

In one instance, an immediate relative (the mother) of a proband with chronic lymphatic leukemia was reported as having had pernicious anemia. In three instances, distant relatives (two paternal aunts and one paternal uncle) were reported as having had pernicious anemia.

In one instance, the mother of a proband with acute myelogenous leukemia was reported as having died of polycythemia vera.

#### THE MALIGNANT TUMOR CONTROL GROUP

The malignant tumor control group is composed of 748 patients, 477 males and 271 females, who served as control and study groups in studies done by the Department of Epidemiology of Memorial Center. All the patients were interviewed by trained interviewers, and the family history was taken in detail. The 748 patients comprising the malignant tumor control group were divided into four "malignant" subgroups. The age, sex and racial distribution of the four subgroups are listed in table 12.

*Subgroup 1:* This group totals 482 patients. All the patients had cancers (but not lymphomas) of the oral cavity. There was no family history of Hodgkin's disease or lymphosarcoma. In two instances, leukemia was reported in the immediate relatives (two sisters). They are listed in table 6.

*Subgroup 2:* This group totals 116 white males with malignant diseases other than those of the oral cavity and lymphomas. There was no family history of Hodgkin's disease, lymphosarcoma or leukemia.

*Subgroup 3:* This group totals 88 white females with rectal cancers. In two instances, immediate relatives (one brother and one sister) had Hodgkin's disease. They are listed in table 8. There was no review of pathology slides at Memorial Center. There was no family history of lymphosarcoma. In one instance, an immediate relative (one sister) had leukemia. She is listed in table 6.

TABLE 12  
Age Distribution in the Malignant Tumor Control Group

	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+	Total
Subgroup 1									
Males				9	44	114	148	46	361
Females				8	30	35	31	17	121
Subgroup 2									
All males				3	17	38	44	14	116
Subgroup 3									
All females				5	25	25	21	12	88
Subgroup 4									
All females				6	22	15	16	3	62

Total: 748—All White

Males: 477

Females: 271

*Subgroup 4:* This group totals 62 white females with cancers other than those of the breast and rectum, and without lymphoma. There was no family history of Hodgkin's disease or lymphosarcoma. In one instance, an immediate relative (the father) had leukemia. He is listed in table 6.

#### THE BENIGN DISEASE CONTROL GROUP

The benign disease control group is composed of a total of 688 patients, 269 males and 419 females, stemming from four subgroups. The age, sex and racial distribution in each subgroup are given in table 13.

*Subgroup 1:* This subgroup is made up of the case histories of 372 patients who had benign diseases. The case histories were selected at random from the inactive files of the Memorial Center Medical Records Library. All of these patients had diseases that were unequivocally benign, such as cervicitis, benign prostatic hypertrophy, pulmonary tuberculosis, cystitis,

TABLE 13  
Age Distribution in the Benign Disease Control Group

	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+	Total
Subgroup 1									
Males	10	33	67	10	12	23	15	8	178
Females	13	18	103	17	28	12	3	0	194
Subgroup 2									
All females				26	44	39	8		117
Subgroup 3									
All females				18	30	37	17	6	108
Subgroup 4									
All males				3	14	27	37	10	91

Total: 688

Males—269    White—662

Females—419    Negro—24

                 Oriental—1

                 American Indian—1

bronchitis, etc. Cases where the diagnosis could be considered as precancerous were excluded. The standards for acceptance of these case histories were approximately the same as those used for the other groups, and most of the patients had a detailed examination at the Memorial Center diagnostic clinic, where the questionnaire in use included questions on familial neoplastic diseases.

One immediate relative (the father) in this group was reported as having died of Hodgkin's disease. He is listed in table 8. The slides could not be located for review at Memorial Center. No cases in the distant family were reported.

No cases of lymphosarcoma in the immediate or distant family were reported in this group.

In five instances, immediate relatives were reported as having died of leukemia (three mothers, one father and one sister). They are listed in table 6. In three instances, distant relatives were reported as having leukemia.

*Subgroup 2:* This group is composed of 117 white females from the Strang Clinic of Memorial Center. In none of these patients was there any evidence of disease. There was no history of Hodgkin's disease or lymphosarcoma in their families. One father died of mycosis fungoides. One immediate relative (a sister) died of leukemia and is listed in table 6. Two distant relatives (one niece and one maternal aunt) allegedly had leukemia.

*Subgroup 3:* This group is composed of 108 white females. All had benign diseases. In one instance, the patient's mother died of Hodgkin's disease. The slides were not reviewed at Memorial Center. The case is listed in table 8. In two other instances, two immediate relatives (mother and son) had leukemia. They are listed in table 6.

*Subgroup 4:* This group is composed of 91 white males. All had benign diseases. There was no incidence of Hodgkin's disease, lymphosarcoma or leukemia in the immediate families.

Subgroups 2, 3 and 4 were taken from the files of the Department of Epidemiology of Memorial Center.

#### OCCURRENCE OF LYMPHOMAS IN NONBLOOD RELATIVES

The occurrence of lymphomas in husbands and wives and in other non-blood relatives of patients with lymphomas, although probably merely medical curiosities, has nevertheless aroused some speculations as to the possibility of the transmission of the disease from man to man.

In Hodgkin's disease, the question of transmission from man to man was first raised by Obratzow.<sup>84</sup> Further interest in this problem was stirred by cases reported in the literature of two surgeons who developed Hodgkin's disease, apparently as a result of accidental inoculation during surgery on patients with Hodgkin's disease and died one month later of the same disease,<sup>28, 50</sup> and certain cases of marital Hodgkin's disease. There is also

a report of marital leukemia in the literature.<sup>85</sup> Similar cases in other forms of cancer have been reported, and raise the question of whether cancer is a communicable disease.<sup>86</sup>

In this study, seven cases involved patients and nonblood relatives who developed lymphomas. In four cases, the patients had Hodgkin's disease and their husbands had leukemias. In two cases, the patients had Hodgkin's disease and their fathers-in-law had lymphosarcoma. In one case, the patient had leukemia, his brother had Hodgkin's disease, and his brother-in-law also had leukemia. In several cases in the lymphoma groups, the patient had had "close contact" with patients with lymphomas before he developed the disease.

Nonblood relatives often share the same environment. This is especially the case with husbands and wives, who share the same environment for the greater part of their lives. Thus, when comparing the familial occurrence of a disease in blood and nonblood relatives, we may find evidence pertaining to the relative importance of environment and heredity. In this study, we do not have enough data to elaborate any hypotheses.

#### STATISTICAL ANALYSIS OF THE DATA

##### 1. *Familial Hodgkin's Disease*

###### A. Chi-square test.

The chi-square test was first applied to the five groups mentioned earlier: the Hodgkin's disease group and the lymphosarcoma, leukemia, malignant tumor and benign disease control groups. Taken collectively ( $n = 4$ ), the groups were tested for "proved" and "proved and not proved" cases of familial Hodgkin's disease. The corresponding values were 27.07 and 20.17, which are highly significant at the 1% level.<sup>87</sup> Thus, the possibility that the different familial occurrence in the control and study groups has occurred by chance is less than 1%.

The study group was then divided into males and females above and below 40 years of age, and the familial occurrence was tested with the chi-

TABLE 14

Comparison of Familial Occurrence of Hodgkin's Disease in the Different Subgroups of the Study Group by the Application of the Chi-Square Test

Subgroup	Value	Significance
1. Males below 40 compared to males above 40—"proved" cases	0.00	Not significant
2. Females below 40 compared to females above 40—"proved" cases	0.15	Not significant
3. Males compared to females, "proved" cases	0.05	Not significant
4. As No. 1, but with "proved and not proved" cases	0.39	Not significant
5. As No. 2, but with "proved and not proved" cases	0.15	Not significant
6. As No. 3, but with "proved and not proved" cases	0.05	Not significant

TABLE 15  
Chi-Square Test in "Proved" Cases of Familial Hodgkin's Disease

Comparison Group	Chi-Square Value	Significance
1. Lymphosarcoma control group	9.64	S*
2. Leukemia control group	2.79	NS
3. Malignant tumor control group	8.95	S*
4. Benign disease control group	8.12	S*

$n = 1$  in all groups; S = Significant; NS = Not Significant.

The chi-square test was applied separately to each control group (1 through 4) and the study group.

\*  $P = 0.01$ .

square test within the group to see if there were significant differences. As is seen in table 14, the six chi-square values were not significant at the 5% level.<sup>87</sup> The subgroups were therefore dropped, and the familial occurrence in the study group as a whole was tested separately, with each control group as a whole ( $n = 1$ ).

With the exception of the leukemia group, the values given in tables 15 and 16 are highly significant, the possibility that the higher concentration of familial Hodgkin's disease in the study group has occurred by chance being less than 1%.<sup>87</sup>

In the leukemia group, when testing with "proved" cases, i.e., zero, the value was not significant, probably because the sample was small (220 patients). When testing with "proved and not proved" cases (two cases), the values again were not significant.

Since the sample is small, any conclusions can be only tentative. It seems that in this study, however, the occurrence of Hodgkin's disease in the immediate family of leukemia patients is as common as its occurrence in the relatives of Hodgkin's probands.

The approximate incidence of familial occurrence in the groups is 1 to 1.5% in the Hodgkin's and leukemia groups and 0.3% in the other groups.

The "rough risk" for the immediate relatives of Hodgkin's disease probands seems to be three times as great as the corresponding risk for the immediate relatives of a proband without the disease. We say "rough risk" because the groups are not "age adjusted."

B. For further clarification, we used an alternate method.

If we were given the age of each immediate relative (parents, siblings and children) of each proband with Hodgkin's disease, we could find the

TABLE 16  
Chi-Square Test in "Proved" and "Not Proved" Cases of Familial Hodgkin's Disease

Comparison Group	Chi-Square Value	Significance
1. Lymphosarcoma control group	11.12	S*
2. Leukemia control group	0.61	NS
3. Malignant tumor control group	7.72	S*
4. Benign disease control group	7.00	S*

$n = 1$  in all groups; S = Significant; NS = Not Significant.

The chi-square test was applied separately to each control group (1 through 4) and the study group.

\*  $P = 0.01$ .

"average" years per family for probands with Hodgkin's disease. If this was 150 years (an "average" estimation), we would then multiply by the yearly occurrence of Hodgkin's disease in the United States (approximately 3,400 cases),<sup>25, 38, 74, 88</sup> and then divide by the total United States population (160,000,000). We would then find:

$$\frac{150 \times 3,400}{160,000,000} = \frac{1}{300}$$

This means that in every 300 patients in study or control groups, we should find one case of Hodgkin's disease in the immediate relatives. This is the case in the lymphosarcoma, malignant tumor and benign disease groups (table 8). The same is true in the leukemia group when testing with "proved" cases. In the study group, we would expect to find three or four cases. However, we have 13 "proved" and 18 "proved and not proved" cases, which implies that the occurrence of Hodgkin's disease in the immediate relatives of probands with Hodgkin's disease is three or four times higher than in the other groups.

In the leukemia group, when testing with "proved and not proved" cases, we reached the same tentative conclusion as that in the chi-square test.

## 2. *Familial Lymphosarcoma*

The chi-square test was also applied to the familial occurrence of lymphosarcoma in the five groups taken all together ( $n = 4$ ). The value is 5.49, which is not statistically significant at the 5% level.<sup>87</sup> Furthermore, there is "disorder" in the occurrence of familial lymphosarcoma in the five groups which supports the insignificance of the familial occurrence.<sup>87</sup> The insignificant familial concentration in lymphosarcoma found in our study is in accord with the reports of familial lymphosarcoma in the literature.

In applying the chi-square test, no distinction was made between "proved" and "not proved" cases.

## 3. *Familial Leukemia*

As in lymphosarcoma, the familial occurrence of leukemia in patients' immediate relatives was tested by the chi-square test in the five groups taken together ( $n = 4$ ). The value is 8.98, which is not significant at the 5% level.<sup>87</sup> Here, the "disorder" is perfectly clear. One would expect to find the highest familial concentration of leukemia in the leukemia group, the next highest in the lymphosarcoma group (as lymphosarcoma so often terminates in leukemia), the next in the Hodgkin's disease group, then in the malignant tumor group, and, finally, the least concentration in the benign disease group.

Clearly, this is not the case (table 6). In this study, no significant differences were found in the familial concentration of leukemia. This is

in accord with the results of the review of Videbaek's material by Busk,<sup>9, 10</sup> despite the abundant reports of familial leukemia in the literature.<sup>7, 89-95 \*</sup>

### DISCUSSION

"... Statistics are dangerous things . . ."—F. W. Stewart<sup>96</sup>

The study of twins and the epidemiologic investigation of families are the two available methods for the study of familial concentration in human diseases. In the investigations of human oncology, however, the value of twin studies has not been established.

The epidemiologic investigation of families should provide evidence about the statistical significance of the familial concentration of the disease in the immediate relatives (those of first degree relationship) of the probands.

The established methodology includes the study and control groups. The study group should be of sufficient size and representative of the "universe." Ideally, the control group should be similar to the study group in all characters except the one under study. As this is never the case, the results of epidemiologic studies are often subject to criticism, and must be considered with reservation and caution.

In this study, a group of 1,102 patients from Memorial Center with histopathologically proved Hodgkin's disease is compared with four control groups, all derived from the Memorial Center population, in order to make the similarities among them more likely. The whole study, involving a total of 4,027 individuals, includes patients with Hodgkin's disease (serving as the study group), and patients with lymphosarcoma, leukemia, other malignant tumors, and benign diseases (serving as control groups). The applied methodology, the effort to identify and verify familial cases of lymphoma, and the quality of the case histories used were approximately the same for all groups. The familial occurrence of lymphomas was tested by the chi-square method. The chi-square results in testing "proved" and "proved and not proved" cases of familial Hodgkin's disease were quite identical.

The results of our study in familial Hodgkin's disease indicate that the occurrence is statistically significant. The possibility that the higher familial concentration in the study groups, as compared to the control groups, has occurred by chance is less than 1%. Due to the great differences in the age distribution of our series, it is hard to be precise as to the magnitude of the familial effect. Roughly speaking, the probability that immediate relatives of a proband with Hodgkin's disease will also have the disease is three times as great as the corresponding probability for the immediate relatives of a proband without the disease.

\* In the statistical analysis in this study, no distinction was made as to the type of leukemia. The clinical experience in this institution, however, is that chronic lymphatic leukemia does occur in families.

Although the familial concentration in Hodgkin's disease is statistically significant, it is really not very high, as only a little more than 1% of the probands with Hodgkin's disease have an immediate relative with the disease. In this respect, Hodgkin's disease resembles most of the instances of reported familial human cancer, such as cancer of the breast, uterus, stomach and esophagus. These cases of familial human cancer have to be clearly differentiated from the rare instances of human tumors where the familial concentration is really high, namely, retinoblastoma, familial intestinal polyposis, xeroderma pigmentosum and multiple neurofibromatosis. In retinoblastoma, the children of the probands with the disease run a 50:50 risk of developing the disease (a figure unusually high for human tumors), and heredity plays a direct and major role.<sup>2, 65, 67</sup>

When the epidemiologic investigation of a disease provides statistical evidence of significant familial concentration, it does not necessarily mean that heredity is the only factor in operation. Apparently, investigators have too often and too easily explained familial concentration in neoplastic diseases in terms of heredity alone. Actually, only in the four abovementioned instances of human tumors with high familial concentration have geneticists unequivocally accepted a major and direct hereditary mechanism.

Where there is a real familial concentration in any given disease, the possibilities are that heredity, environment,\* or a combination of both, are operating. Geneticists believe that in genetics generally, and in cancer specifically, the purely genetic and purely environmental characters are not really sharply differentiated, and there is no absolute dichotomy between extrachromosomal and chromosomal factors.

In the experimental field, it has been shown in mammary carcinoma in mice that the genetic constitution plays an important role in determining the results of the "virus infection."<sup>68</sup>

Gorer expresses the belief ("... no better than a guess...") that in familial human neoplasias, environment is the main factor.<sup>2</sup>

The familial cases in this study were examined as to similarities in the time of onset of the disease, similarities in the age at onset of the disease, similarities in the environment, and similarities in the location of the disease at onset. The time and age at the "apparent" onset of the disease in 13 "proved" cases of familial Hodgkin's disease are given in table 17. In two cases there are similarities in the age at onset, in seven cases there are similarities in time of onset, in one case there are similarities in both, and in three cases there are no similarities. In some cases, notably, family 2, J. M., the similarities in the environment, time of onset, and location of the disease at onset are quite striking.

Hodgkin's disease apparently does not have a simple inheritance, as the familial concentration is low. From this study, heredity seems to play an

\* Environment, as used in this study, includes everything except heredity and the "causative factors."

indirect or minor role in the etiology of Hodgkin's disease. In the familial cases it is not possible to determine whether the concentration is actually the consequence of heredity, or of the greater environmental similarities for the members within the family. However, from this study the familial concentration observed would appear to result more probably from the family environment than from hereditary factors.\* In family 2, J. M., mother and son living under an unusually similar environment developed the disease the same week in the same place (left neck). Similar although less impressive cases are included in this study and are reported in the literature. Yet we cannot claim to have established the relative importance of heredity and environment in Hodgkin's disease. In this study, it has been shown that in the immediate relatives of probands with Hodgkin's

TABLE 17  
Age and Time of Apparent Onset of Disease in Probands and Relatives  
of 13 Cases of Proved Familial Hodgkin's Disease

Family	Age at Onset		Time of Onset	
	Proband	Relative	Proband	Relative
1	35	(1) 23 (2) 34	Dec. 1939	(1) March 1932 (2) 1935
2	38	20	Aug. 1954	Sept. 1954
3	30	37	Jan. 1951	March 1954
4	14	52	June 1952	End of 1952
5	38	40	June 1956	Spring 1934
6	38	"Elderly"	Aug. 1950	Summer 1948
7	24	36	April 1952	? 1951
8	24	22	End of 1951	End of 1951
9	52	46	1923	Feb. 1952
10	40	13	Beginning of 1950	Summer 1955
11	47	19	Dec. 1947	Aug. 1948
12	50	40	Feb. 1953	Aug. 1954
13	53	16	April 1953	Sept. 1955

disease the risk of developing Hodgkin's disease is three times as great as the corresponding risk for immediate relatives of probands without the disease. This observation might well imply a major role for heredity. If heredity is responsible for the familial concentration in Hodgkin's disease in the present study, the genetic mechanism must be extremely complex.

We did not expect—nor did we obtain—evidence as to the etiology of Hodgkin's disease from this study. One cannot expect to discover the etiology of a disease with statistics, and the not uncommon practice of labeling epidemiologic papers with "the etiology of . . ." is incorrect and misleading. "In cancer one cannot realistically expect to do more (by using epidemiological methods) than to identify factors frequently associated with

\* In a previous study by Levitan and us on the ABO blood group distribution in Hodgkin's disease,<sup>29</sup> differences as compared to blood group distribution in control groups were demonstrated. This would favor hereditary involvement in Hodgkin's disease. However, the results were considered to be only tentative.

cancer. The proof of an etiological relationship must then be sought through more intensive clinical and experimental studies."<sup>7,8</sup> However, similarities in the time of "apparent" onset of disease (unrelated to age, see table 17) in the affected relatives suggest that "infectious agents" may be involved in the etiology of Hodgkin's disease.

Though the familial concentration in Hodgkin's disease is low, physicians should be alert to the possibility of "potential" cases in the relatives of Hodgkin's disease patients in the interest of early detection and, consequently, more efficient treatment.

The familial concentration of lymphosarcoma and leukemia was also examined in this study, and no statistically significant differences were found. As has been discussed previously, this is in accord with the recent literature, the reports of familial lymphosarcoma in the literature, and the analysis of Videbaek's study of familial leukemia by Busk.<sup>9,10</sup>

#### SUMMARY AND CONCLUSIONS

1. From the present study it appears that Hodgkin's disease occurs in families more often than one might expect from chance coincidence.

2. Due to the great differences in the age distribution in our series, it is hard to be precise about the magnitude of the familial effect. Roughly speaking, the probability that the immediate relatives of a proband with Hodgkin's disease will also develop the disease is three times as great as the corresponding probability for the immediate relatives of a proband without the disease.

3. Familial concentration in Hodgkin's disease, though statistically significant, is not very high. In this respect, the situation in Hodgkin's disease resembles most of the instances of reported familial human cancer.

4. Hodgkin's disease apparently does not have a simple inheritance. From this study, heredity seems to play a relatively minor or indirect role in the etiology of Hodgkin's disease.

5. Whether the familial concentration observed here is actually the consequence of heredity, or of the greater environmental similarities for the members within the family cannot be determined. The evidence, however, points more to environment than to heredity.

6. Similarities in the time of onset of Hodgkin's disease (unrelated to age) in the affected relatives suggest the importance of "infectious agents."

7. No statistically significant differences were found for familial leukemia and lymphosarcoma.

#### ADDENDUM

In the following families, all the probands have histopathologic diagnoses confirmed by the Department of Pathology of Memorial Center. Where the diagnosis of a relative was not confirmed at Memorial Center, the diagnosis has been placed within quotation marks.

*Family 1.* Proband: W. R., a 35 year old white male of Italian descent. The apparent date of onset of the disease was December, 1939. He died at home in February, 1944. There was no autopsy. Left axillary node biopsy: Hodgkin's disease.

Relatives: 1. Patient's sister, C. J., 23 year old housewife. The apparent onset of the disease was in March, 1932. She was treated for the disease at Presbyterian Hospital in New York City in 1933. Node biopsy reviewed at Memorial Center: Hodgkin's disease. 2. Another sister, L. I., 34 year old housewife. Developed Hodgkin's disease in 1935. Cervical node biopsy performed by her family physician. Review of slides at Memorial Center: Hodgkin's disease.

It is worth while to notice in this case the development of the disease in two siblings, and the similarities in the age at onset of the proband and the second sibling.

*Family 2.* Proband: J. M., 38 year old white female of Italian descent. The apparent onset of the disease was in August, 1954, with left cervical lymphadenopathy. She is now being treated at Memorial Center. Node biopsy: Hodgkin's granuloma.

Relative: Patient's son, A. M., 20 year old white male. Works with his mother in dressmaking. Striking environmental similarities in mother and son. Apparent onset of the disease was one week after onset in mother (September, 1954), with the same location, left cervical lymphadenopathy. Now being treated at Memorial Center. Node biopsy: Hodgkin's granuloma.

In this case, the similarities in the time of onset, location of disease at onset, and environment are quite striking.

*Family 3.* Proband: A. D., 30 year old white male of Italian descent. The apparent onset of the disease was in January, 1951. The patient died in 1956. No autopsy was performed. Left axillary node biopsy: Hodgkin's granuloma.

Relative: Brother, A. D., 37 year old white male. The apparent onset of the disease was in March, 1954. Died in May, 1957. An autopsy was performed. Left neck node biopsy: Hodgkin's granuloma.

*Family 4.* Proband: A. M., 14 year old white male of Hungarian-Jewish descent. The apparent onset of the disease was in June, 1952. Now being treated at Memorial Center. Neck node biopsy reviewed at Memorial Center: Hodgkin's granuloma.

Relative: Mother, S. M., 52 year old housewife. Past history: Weber-Christian disease and positive serologic test for syphilis (STS) in 1945 (Mt. Sinai Hospital, New York). The STS of the proband was negative. Apparent onset of the disease was at the end of 1952. Died in May, 1953. No autopsy was performed. Pathology slides of a lymph node biopsy were submitted to Memorial Center from Mt. Sinai Hospital and were diagnosed as Hodgkin's disease.

It is worth while to note that both proband and relative developed the disease at approximately the same time.

*Family 5.* Proband: L. S., 38 year old white female of mixed European descent. Apparent onset of the disease was in June, 1956. Now being treated at Memorial Center. Lymph node biopsy: Hodgkin's granuloma.

Relative: Father, G. B., 40 year old white male. Summary submitted from Massachusetts General Hospital, Boston, Massachusetts. Apparent onset of disease was in the spring of 1934. Died in October, 1934. No autopsy. Lymph node biopsy reviewed at Memorial Center. Hodgkin's granuloma.

*Family 6.* Proband: B. P., 38 year old white female, American Jew. Apparent onset of the disease was in August, 1950. Now being treated at Memorial Center. Lymph node biopsy: Hodgkin's disease.

Relative: Mother, A. P. Abstracts received from the Jewish Hospital of Brooklyn, N. Y., and the New York Post-Graduate Hospital, New York, described her as an "elderly" white woman. Apparent onset of the disease was in the summer of 1948. Died in 1952. An autopsy was performed at the Jewish Hospital of Brooklyn. Pathology slides were reviewed at Memorial Center. Diagnosis: Hodgkin's sarcoma.

A distant relative, the mother's brother, was treated at Regina General Hospital, Regina, Saskatchewan, Canada, for "typical Hodgkin's disease," which he developed in 1933 at the age of 55. The slides were not available for review.

*Family 7.* Proband: M. K., 24 year old white male of Hungarian-Jewish descent. Apparent onset of the disease was in April, 1952. Positive serologic test (STS), was detected in 1946. Now attending Memorial Center Clinics. He has no evidence of activity of the disease. Lymph node biopsy: Hodgkin's granuloma.

Relative: Brother, J. K., 36 year old white male. His first Memorial Center visit was in November, 1956. The apparent date of onset of the disease was difficult to determine. At the age of 24 he developed infectious mononucleosis, with neck and axillary lymphadenopathy. Within a short time all of the nodes had disappeared except for one which persisted high in the right neck. Seven years later this node became enlarged, with no other symptoms or signs. At the end of 1952 the node was biopsied and later diagnosed at Memorial Center as Hodgkin's granuloma. The patient was treated with radical neck dissection and radiotherapy, and remained free of disease until 1954, when a submandibular node developed. The biopsy of this node, interestingly enough, was read as Hodgkin's paraganuloma. The new node was treated with radiotherapy, and today the patient is well and apparently free of disease.

Both brothers had Hodgkin's disease, Class I, and responded well to local therapy.

*Family 8.* Proband: R. H., 24 year old white male. Apparent onset of the disease was at the end of 1951. Lymph node biopsy: Hodgkin's disease. A second node biopsy was performed and diagnosed as Hodgkin's granuloma.

Relative: Sister, C. H., 22 year old white female. Apparent onset of the disease was at the end of 1951. Lymph node biopsy: Hodgkin's granuloma.

Note similarities in the time of onset of the disease.

*Family 9.* Proband: H. S., 52 year old white male. Apparent onset of the disease was in 1923. Died in 1924. Lymph node biopsy performed in 1923 and reviewed in 1958 was read as Hodgkin's disease and Hodgkin's paraganuloma, respectively.

Relative: Son, J. S., 46 year old white male. Apparent onset of the disease was in February, 1952. Lymph node biopsy: Hodgkin's granuloma.

*Family 10.* Proband: S. S., 40 year old white female, Lithuanian Jew. Apparent onset of the disease was at the beginning of 1950. Died in 1954. No autopsy. Lymph node biopsy: Hodgkin's granuloma.

Relative: Son, A. S., 13 year old white male. Apparent onset of the disease was in the summer of 1955. Attending Memorial Center Clinics at present. Lymph node biopsy: Hodgkin's granuloma.

*Family 11.* Proband: M. S., 47 year old white female of Polish descent. Apparent onset of the disease was in December, 1947. Died in July, 1958. Lymph node biopsy: Hodgkin's granuloma. An autopsy performed at Memorial Center showed secondary amyloidosis but no evidence of Hodgkin's disease.

Relative: Daughter, D. S., 19 year old white female. Apparent onset of the disease was in August, 1948. Had Hodgkin's disease, Class III,\* at the time of her first Memorial Center admission. In March, 1949, the patient developed paraplegia due to Hodgkin's disease, and in 1951 she showed signs of an intracranial tumor compressing the brain. Brain surgery was performed at New York Hospital, New York City. The tumor was removed, the brain irradiated, and complete subjective and objective recovery followed. Ten years after the onset of the disease she is married and doing well. She is attending the Memorial Center Clinic. Review of the pathology slides: Hodgkin's granuloma.

Note similarities in the time of onset.

*Family 12.* Proband: P. M., 50 year old white male. Apparent onset of the disease was in February, 1953. Died in 1957. Lymph node biopsy: Hodgkin's disease.

Relative: Sister, G. B., 40 year old white female. Summary submitted from Monmouth Memorial Hospital, Long Branch, New Jersey. Apparent onset of the disease was in August, 1954. Died in April, 1955. Lymph node biopsy reviewed at Memorial Center: Hodgkin's sarcoma.

*Family 13.* Proband: P. P., 53 year old white male, native of Greece. Apparent onset of the disease was in April, 1953. Lymph node biopsy reviewed at Memorial Center: Hodgkin's granuloma.

Relative: Daughter, I. P., 16 year old white female. Apparent onset of the disease was in September, 1955. Lymph node biopsy reviewed at Memorial Center: Hodgkin's granuloma.

*Family 14.* Proband: C. B., 31 year old white male of Italian descent. Apparent onset of the disease was in March, 1944. Lymph node biopsy: Hodgkin's paragruloma.

Relative: Brother, M. B., 20 year old white male. Apparent onset of the disease was in November, 1945. Treated for Hodgkin's disease at Munich, Germany, Walter Reed Hospital, Washington, D. C., and Memorial Center. A review of the original lymph node biopsy taken in Germany showed "intensive eosinophilia of node and fibrosis of capsule but not diagnostic of Hodgkin's disease."

*Family 15.* Proband: A. L., 50 year old white female. Apparent onset of the disease was in 1924. Lymph node biopsy: Hodgkin's disease.

Relative: Father, S. W. "Died of Hodgkin's disease in 1897." The diagnosis was made by a Dr. Bartholomew of Philadelphia.

*Family 16.* Proband: S. K., 32 year old white female. Apparent onset of the disease was in 1952. Lymph node biopsy: Hodgkin's disease.

Relative: "... Brother died of Hodgkin's disease."

*Family 17.* Dizygotic twins, both members affected.† Proband: J. W., 29 year old white male. Apparent onset of the disease was in December, 1951. Died in January, 1953. Lymph node biopsy reviewed at Memorial Center: Hodgkin's disease.

Relative: Dizygotic twin brother, J. W. Developed the disease in the summer of 1940 at the age of 18. Died a few months later. Lymph node biopsy read at the

\* According to Craver's classification, Class III is generalized disease, often accompanied by constitutional signs and symptoms such as pruritus, night sweats, fever and anemia.

† The proband in this case was seen privately by one of us (H. D. D.). A detailed case history for each brother was kindly submitted to us by Dr. T. H. Mendell, of Philadelphia, to whom we are greatly indebted.

University of Pennsylvania Hospital as "Hodgkin's disease." The slide was not available for review at Memorial Center.

*Family 18.* Proband: S. B., 18 year old white female. Apparent onset of the disease was in 1956. Lymph node biopsy: Hodgkin's granuloma.

Relative: "... Mother died of Hodgkin's disease in 1937."

*Family 19.* Proband: B. S., 22 year old white female. Biopsy at Memorial Center: Hodgkin's granuloma.

Relative: First cousin, 26 year old white female. Biopsy at Memorial Center: Hodgkin's granuloma.

*Family 20.* Proband: M. S., 35 year old white male. Biopsy at Memorial Center: Hodgkin's granuloma.

Relative: Paternal first cousin, 19 year old white female. Biopsy reviewed at Memorial Center: Hodgkin's disease.

*Family 21.* Proband: T. P., 23 year old white female. Biopsy at Memorial Center: Hodgkin's disease.

Relative: First cousin, 28 year old white male. Biopsy reviewed at Memorial Center: Hodgkin's sarcoma.

*Family 22.* Proband: H. O., 23 year old white male. Biopsy at Memorial Center: Hodgkin's granuloma.

Relative: "One paternal uncle had Hodgkin's disease."

*Family 23.* Proband: P. S., 41 year old white male. Biopsy at Memorial Center: Hodgkin's granuloma.

Relative: "One maternal aunt had Hodgkin's disease."

*Family 24.* Proband: E. M., 26 year old white female. Biopsy at Memorial Center: Hodgkin's granuloma.

Relative: "Her grandmother died of Hodgkin's disease."

*Family 25.* Proband: R. G., 16 year old white male. Biopsy at Memorial Center: Hodgkin's granuloma.

Relative: "Grandmother died some years ago of Hodgkin's disease."

*Family 26.* Proband: H. G., 36 year old white male. Biopsy at Memorial Center: Hodgkin's disease.

Relative: "One paternal great-aunt died of Hodgkin's disease."

*Family 27.* Proband: E. P., 34 year old white male. Biopsy at Memorial Center: Hodgkin's disease.

Relative: "His sister's daughter died of Hodgkin's disease."

*Family 28.* Proband: L. B., 25 year old white male. Biopsy at Memorial Center: Hodgkin's granuloma.

Relative: "Paternal grandfather died of Hodgkin's disease."

*Family 29.* Dizygotic twins, one member affected. Proband: L. G., 34 year old white male. Biopsy and post mortem at Memorial Center: Hodgkin's sarcoma. His fraternal twin brother is alive and well.

*Family 30.* Monozygotic twins, one member affected. Proband: W. G., 55 year old white male. Lymph node biopsy: Hodgkin's disease. His identical twin brother is living and well.

*Family 31.* Proband: B. F., 60 year old white female. Apparent onset of the disease was in February, 1934. Died in 1940. An autopsy was performed. Lymph node biopsy: Hodgkin's granuloma. Postmortem: Hodgkin's disease, Paget's disease, and generalized arteriosclerosis.

Relative: Son, A. F., 43 year old white male. Apparent onset of the disease was in 1938. Died in 1940. An autopsy was performed. Microscopic diagnosis: lymphosarcoma.

*Family 32.* Proband: E. G., 19 year old white female. Apparent onset of the disease was in August, 1954. Biopsy at Memorial Center: Hodgkin's disease.

Relative: Mother, C. G. Died in New Rochelle Hospital, New Rochelle, N. Y., in December, 1946. Slides were reviewed at Memorial Center: reticulum cell sarcoma. According to the chart, "The mother's mother died of cancer of lymphatic origin."

*Family 33.* Proband: G. S., 59 year old white male. Apparent onset of the disease was in January, 1948. Lymph node biopsy: Hodgkin's disease.

Relative: Mother, A. S., 73 year old white female. Apparent onset of the disease was in 1940. Lymph node biopsy: lymphosarcoma.

The proband's brother was a patient at Memorial Center also, and had epidermoid cancer of the tonsil.\*

*Family 34.* Proband: B. S., 22 year old white female. Apparent onset of the disease was in 1952. Lymph node biopsy: Hodgkin's granuloma.

Relative: Brother, L. S. "... Was attended by Professor Frank Forman of the Medical School of the University of Capetown, South Africa, for lymphosarcoma." The slides were not reviewed at Memorial Center.

*Family 35.* Proband: A. F., 43 year old white male. Apparent onset of the disease was in 1938. Died in 1940. An autopsy was performed. Microscopic diagnosis: lymphosarcoma.

Relative: Mother, B. F., 60 year old white female. Apparent onset of the disease was in February, 1934. Died in 1940. An autopsy was performed. Microscopic diagnosis: Hodgkin's granuloma.

*Family 36.* Proband: S. M., 61 year old white male. Apparent onset of the disease was in 1945. Pathologic diagnosis: reticulum cell sarcoma.

Relative: Brother, F. M., who died of Hodgkin's disease at the age of 47 at Lenox Hill Hospital, New York City. Slides reviewed at Memorial Center: Hodgkin's granuloma.

*Family 37.* Proband: N. B., 54 year old white male. Apparent onset of the disease was in 1945. Lymph node biopsy: lymphosarcoma.

Relative: Brother, A. B. Summary submitted from Bronx Veterans Administration Hospital, New York City. He was "treated for Hodgkin's disease" in 1937 at the age of 38. The slides were not available for review at Memorial Center.

There is also a question of whether their sister died of Hodgkin's disease. -

*Family 38.* Proband: H. J., 38 year old white female. Apparent onset of the disease was in 1942. Pathologic diagnosis: lymphosarcoma.

Relatives: Sister, E. K., and nephew, R. B. (sister's son, 17 year old white male). Both had Hodgkin's disease and both were treated at Western Reserve University Hospital, Cleveland, Ohio. The sister's slides were reviewed at Me-

\* In other cases of familial lymphoma, immediate relatives had another form of neoplasia. These cases are not reported in this study.

morial Center in 1942 and, according to a notation in the proband's chart, were read as Hodgkin's disease. Unfortunately, we were unable to locate either the slides or the official pathology report. The nephew's slides were located, however, and submitted for review. Diagnosis: Hodgkin's disease.

*Family 39.* Proband: N. P. Pathologic diagnosis: reticulum cell sarcoma. Relative: "One uncle died of Hodgkin's disease."

*Family 40.* Proband: B. B. Pathologic diagnosis: lymphosarcoma. Relative: "Paternal uncle died of Hodgkin's disease."

*Family 41.* Proband: A. A. Pathologic diagnosis: reticulum cell sarcoma. Relative: "There is a family history of Hodgkin's disease and Cooley's anemia."

*Family 42.* Proband: M. S. Pathologic diagnosis: lymphosarcoma. Relative: "... Brother with lymphosarcoma."

*Family 43.* Proband: E. O. Pathologic diagnosis: lymphosarcoma. Relative: "... Daughter with lymphosarcoma."

*Family 44.* Proband: E. F. Pathologic diagnosis: lymphosarcoma. Relative: "... Brother with lymphosarcoma."

*Family 45.* Proband: S. S. Pathologic diagnosis: reticulum cell sarcoma. Relative: Paternal uncle. Pathologic diagnosis: reticulum cell sarcoma.

*Family 46.* Proband: J. G. Pathologic diagnosis: lymphosarcoma. Relative: "One paternal cousin died of leuko-lymphosarcoma."

*Family 47.* Proband: 70 year old white female with chronic myelogenous leukemia. Relative: Father, "Hodgkin's disease."

*Family 48.* Proband: 65 year old white male with acute myelogenous leukemia. Relative: Brother, "Hodgkin's disease."

*Family 49.* Proband: 62 year old white female with chronic myelogenous leukemia. Relative: Niece, a patient at Memorial Center with proved Hodgkin's disease.

#### ACKNOWLEDGMENTS

We are greatly indebted to Irvin D. J. Bross, Ph.D., Head of the Research Design and Analysis Service, Sloan-Kettering Institute for Cancer Research, New York, for his invaluable help and advice; to Dr. E. L. Wynder, for permission to compose our malignant tumor control group and most of our benign disease control group from his cases on file; to Dr. R. H. Osborne, of the Institute for the Study of Human Variation, Columbia University, New York, for his criticism and advice on the genetic implications of this study; to Dr. B. W. Jaslowitz, for his help and advice in preparing the manuscript; to Miss Mona Jones, for editorial assistance in preparing the manuscript; and to Mrs. Marilyn Leonard and Miss Janice Roth, for secretarial assistance.

#### SUMMARIO IN INTERLINGUA

Esseva interprendite un studio de morbo de Hodgkin familial, con le objectivo de determinar—per le application de methodos epidemiologic—si su occurrentia, i.e. le occurrentia familial de morbo de Hodgkin, es un phenomeno de signification general o un evento sporadic que se manifesta al hasardo. Esseva utilisate quatro representative grupos de controlo consistente de patientes (1) con lymphosarcoma, (2) leucemia, (3) altere canceres, e (4) morbos benigne. Omne le subjectos in le gruppo de studio habeva morbo de Hodgkin verificate per un diagnose histopatho-

logic que habeva essite effectuate per un membro del Departamento de Pathologia al Centro Memorial pro Cancere e Morbos Affin.

Le gruppo de studio consisteva de 1.102 patientes con morbo de Hodgkin. Illes esseva studiate ab le puncto de vista de lor sexo, lor etate, lor racia, e le typologia pathologic de lor morbo, si ben como ab le puncto de vista del constataciones necroptic, del datos statistic de longevitate, e de altere parametros. Esseva investigate le occurrentia de morbo de Hodgkin, lymphosarcoma, e leucemia in le consanguineos del patientes in le gruppo de studio. In iste mesme gruppo le occurrentia familial de tuberculose, diabete mellite, e anemia perniciose esseva evalutate. Simile studios esseva effectuate in le familias del patientes qui constituava le gruppos de controlo. Omne le datos assi colligite esseva analysate statisticamente.

Esseva concludite que morbo de Hodgkin occorre in plure membros del mesme familia con un frequentia non explicabile como coincidentia. In terminos general, immediate consanguineos de subjectos con morbo de Hodgkin curre un triple risco de contraher le morbo in comparison con le immediate consanguineos de subjectos sin morbo de Hodgkin. Viste que le incidentia familial de morbo de Hodgkin non es multo elevate (ben que ancora statisticamente significative), le phenomeno simula le reportate casos de occurrentias familial de cancro human in general.

Il pare que morbo de Hodgkin non es hereditabile per simple transmission genetic. Le studio non determina nettemente si hereditate o milieu es plus importante como factor in le disveloppamento consequential de morbo de Hodgkin, sed le datos disponibile pare incriminar le milieu plus tosto que le hereditate.

Correspondentias in le tempore del declaration de morbo de Hodgkin in gruppos individual de consanguineos suggere le importantia de agentes infectiose.

Nulle statisticamente significative differentias esseva notate in le caso del occurrentia familial de lymphosarcoma e leucemia.

#### BIBLIOGRAPHY

1. MacDonald, E. J.: Historical trends in cancer, in *Cancer. A manual for practitioners*, 3rd Ed., 1956, American Cancer Society (Massachusetts Division), Inc., Boston, p. 1.
2. Gorer, P. A.: *Cancer, in Clinical genetics*, edited by Sorsby, A., 1953, C. V. Mosby Co., St. Louis, p. 558.
3. Brobeck, O.: Heredity in cancer uteri: a genetical and clinical study of 200 patients with cancer of the cervix uteri and 90 patients with cancer of the corpus uteri, 1949, Universitets forloget, Aarhus, Denmark.
4. Jacobsen, O.: Heredity in breast cancer: a genetic and clinical study of 200 probands, 1946, H. K. Lewis & Co., Ltd., London.
5. Murphy, D. P.: Heredity in uterine cancer, 1952, Harvard University Press, Cambridge.
6. Videbaek, A.: Familial leukemia. A preliminary report, *Acta med. Scandinav.* 127: 26, 1947.
7. Videbaek, A.: Heredity in human leukemia and its relation to cancer, 1947, H. K. Lewis & Co., Ltd., London.
8. Macklin, M. T.: The role of heredity in gastric and intestinal cancer, *Gastroenterology* 29: 507, 1955.
9. Busk, T.: Genetical studies in leukemia, 1952, Proceedings of the 2nd National Cancer Conference, American Cancer Society, New York, p. 1087.
10. Clemmensen, J., and Sorensen, J.: Malignant neoplasms of haemopoietic and connective tissues in various countries. Cancer incidence in Denmark 1943 to 1953 V, *Danish M. Bull.* 5: 73, 1958.
11. Gorer, P. A., in a review of Videbaek, *Ann. Eugenics* 14: 346, 1949.
12. Videbaek, A., and Mosbech, J.: The aetiology of gastric carcinoma elucidated by a study of 302 pedigrees, *Acta med. Scandinav.* 149: 137, 1954.

13. Kaplan, I. I.: Carcinoma of the breast in one of homologous twin sisters, *Am. J. M. Sc.* **190**: 331, 1935.
14. McFarland, J., and Meade, T. S.: The genetic origin of tumors, supported by their simultaneous and symmetrical occurrence in homologous twins, *Am. J. M. Sc.* **184**: 66, 1932.
15. Macklin, M. T.: An analysis of tumors in monozygous and dizygous twins. Report of 15 unpublished cases, *J. Hered.* **31**: 277, 1940.
16. Peyron, A., and Kobozieff, N.: Les tumeurs chez les jumeaux, *Bull. Assoc. franç. p. l'étude du cancer* **26**: 93, 1937.
17. Dunn, L. C.: *Genetics in the 20th Century*, 1951, The Macmillan Co., New York.
18. Macklin, M. T.: Heredity and constitution in disease, in *Pathology*, 3rd Ed., Chapter 45, Edited by Anderson, W. A., 1957, The C. V. Mosby Co., St. Louis.
19. Stern, C.: *Principles of human genetics*, 1949, W. H. Freeman & Co., San Francisco.
20. Peacocke, G.: Hodgkin's disease occurring in twins, *Dublin J. M. Sc.* **120**: 85, 1905.
21. Remde, W.: Über konkordantes Auftreten von Lymphogranulomatose bei einigen Zwillingen, *Innere Med.* **5**: 15, 1950.
22. Charache, H.: Tumors in one of homologous twins. Hodgkin's disease, osteogenic sarcoma, *Am. J. Roentgenol.* **46**: 69, 1941.
23. Charache, H.: Tumors in one of homologous twins. Hodgkin's disease with primary skeletal manifestations, *Am. J. Roentgenol.* **54**: 179, 1945.
24. Charache, H.: Hodgkin's disease in children, *New York State J. Med.* **46**: 507, 1946.
25. Hoster, H. A., and Dratman, M. B., edited by Craver, L. F., and Rolnick, H. A.: Hodgkin's disease, 1832-1947, *Cancer Research* **8**: 1, 1948.
26. Allan, G. A., and Blacklock, J. W. S.: Hodgkin's disease with paraplegia, *Glasgow M. J.* **103**: 115, 1925, cited by Wallhauser, A.: Hodgkin's disease, *Arch. Path.* **16**: 522, 1933; **16**: 672, 1933.
27. Arkin, A.: Familial mediastinal lymphogranuloma, *Am. J. M. Sc.* **171**: 669, 1926.
28. Bonati, F.: Clinical and statistical findings in Hodgkin's disease, *Gior. di clin. med.* **31**: 746, 1950.
29. Branch, C. F.: A case of congenital lymphoblastoma, *Am. J. Path.* **9**: 777, 1933.
30. Brennan, M. J.: Personal communication to DeVore, J. W., and Doan, C. A.<sup>38</sup>
31. Bunting, C. H., and Yates, J. A.: An etiologic study of Hodgkin's disease—preliminary note, *J. A. M. A.* **61**: 1803, 1913.
32. Burnam, C. F.: Hodgkin's disease with special reference to its treatment by irradiation, *J. A. M. A.* **87**: 1445, 1926.
33. Chiari, H.: Personal communication to Mallory, G. K., cited by Branch, C. F.<sup>29</sup>
34. Davis, P. L.: Personal communication to Mazar, S. A., and Strauss, B.<sup>50</sup>
35. DeCandia, S.: Morbo di Hodgkin familiare, *Clin. nuova* **2**: 234, 1936.
36. Degen, H.: Ein Beitrag zur Lehre vom Lymphosarcom, *Inaug. Diss.*, 1886, S. Abel, Greifswald, cited by Arkin, A.<sup>27</sup>
37. Desjardins, A. V.: The etiology of lymphoblastoma, *J. A. M. A.* **103**: 1033, 1934.
38. DeVore, J. W., and Doan, C. A.: Studies in Hodgkin's syndrome. XII. Hereditary and epidemiological aspects, *Ann. Int. Med.* **47**: 300, 1957.
39. Galloway, J.: Hodgkin's disease, *Brit. M. J.* **2**: 1201, 1922.
40. Gilbert, R.: Radiotherapy in Hodgkin's disease (malignant granulomatosis). Anatomic and clinical foundations; governing principles; results, *Am. J. Roentgenol.* **41**: 198, 1939.
41. Gordon, M. H., Gow, A. E., Levitt, W. M., and Weber, F. P.: Recent advances in the pathology and treatment of lymphadenoma, *Proc. Roy. Soc. Med.* **27**: 1035, 1934.
42. Heussi, M.: Ueber Lymphogranulomatose besondere ihr familiäres Vorkommen, 1936, Fluntern, Zürich.
43. Jackson, H., Jr., and Parker, F., Jr.: *Hodgkin's disease and allied disorders*, 1947, Oxford University Press, New York.

44. Kaplan, I. I.: Hodgkin's disease in childhood, *Arch. Pediat.* **51**: 325, 1934.
45. Kasdon, S. C.: Pregnancy and Hodgkin's disease with a report of three cases, *Am. J. Obst. and Gynec.* **57**: 282, 1949.
46. Koranyi, A., discussion to Borday: Einführungen in der pathologischen Anatomie und Histopathologie der Lymphogranulomatosis, *Klin. Wchnschr.* **1**: 466, 1930, cited by Hoster, H. A., and Dratman, M. B.<sup>25</sup>
47. LaPorte, D.: Maladie de Hodgkin familiale, *Presse méd.* **44**: 651, 1936.
48. Leutkons, K.: Statistische und histologische Betrachtungen über die Hodgkinschen Granulomatose, *Inaug. Diss.*, 1934, Freiberg, cited by Remde, W.<sup>21</sup>
49. McHeffey, G. J., and Peterson, R. F.: Hodgkin's disease occurring simultaneously in two brothers, *J. A. M. A.* **102**: 521, 1934.
50. Mazar, S. A., and Straus, B.: Marital Hodgkin's disease, *Arch. Int. Med.* **88**: 819, 1951.
51. Morowitz, P.: Rassenhygiene und Bevölkerungspolitik. Erbliche und konstitutionelle Faktoren bei einigen Blutkrankheiten, *München. med. Wchnschr.* **83**: 2073, 1936.
52. Pfander, U.: Lymphogranulomatose Hodgkin et disposition héréditaire, Lausanne, 1948, cited by DeVore, J. W., and Doan, C. A.<sup>38</sup>
53. Priesel, A., and Winkelbauer, A.: Placentarübertragung des Lymphgranuloms, *Virchows Arch. f. path. Anat.* **262**: 749, 1926, cited by Kasdon, S. C.,<sup>45</sup> and Cutler, M., and Buschke.<sup>62</sup>
54. Sandick, H.: Hodgkin's disease involving the stomach, *Gastroenterology* **15**: 135, 1950.
55. Schier, W. W.: Familial Hodgkin's disease, *Blood* **9**: 236, 1954.
56. Senator, H., in *Deutsche Klinik* **3**: 373, 1903, cited by Arkin, A.<sup>27</sup>
57. Smith, C. A.: Hodgkin's disease in childhood. A clinical study with a resumé of the literature to-date, *J. Pediat.* **4**: 12, 1934.
58. Videbaek, A.: Familial Hodgkin's disease, *Acta haemat.* **14**: 200, 1955.
59. Uddstromer, M.: On the occurrence of lymphogranulomatosis in Sweden, 1915-1931, and some considerations as to its relation to tuberculosis, *Acta tuberc. Scandnav. Supp.* **1**: 1-225, 1934.
60. Warner, E. C.: The treatment of lymphadenoma with a sensitized vaccine of the elementary body, *Lancet* **2**: 417, 1936.
61. Weinstein, A.: Personal communication to DeVore, J. W., and Doan, C. A.<sup>38</sup>
62. Cutler, M., and Buschke, F., assisted by Cantril, S.: *Cancer. Its diagnosis and treatment*, 1939, W. B. Saunders Company, Philadelphia.
63. Hennessy, J. P., and Rottino, A.: Hodgkin's disease in pregnancy with a report of twelve cases, *Am. J. Obst. and Gynec.* **63**: 756, 1952.
64. Southam, C. M., Diamond, H. D., and Craver, L. F.: Pregnancy during Hodgkin's disease, *Cancer* **9**: 1141, 1956.
65. Homburger, F.: *The biologic basis of cancer management*, 1st Ed., 1957, Hoeber-Harper, New York.
66. Burger, R. E., and Lehman, E. P.: Hodgkin's disease—a review of fifty-four cases, *Arch. Surg.* **43**: 839, 1941.
67. Goldman, L. B.: Hodgkin's disease. An analysis of 212 cases, *J. A. M. A.* **114**: 1611, 1940.
68. Bross, I. D. J.: Personal communication.
69. MacDonald, E. J.: The present incidence and survival picture in cancer and the promise of improved prognosis, *Bull. Am. Coll. Surgeons* **33**: 75, 1948.
70. McMahon, B.: Epidemiological evidence on the nature of Hodgkin's disease, *Cancer* **10**: 1045, 1957.
71. Bersack, S.: Hodgkin's disease. Incidence and prognosis, *Arch. Int. Med.* **73**: 233, 1944.
72. *Cancer in Connecticut 1935-1951*, Connecticut State Department of Health, 1955.
73. Dorn, H. F., and Cutler, S. J.: Morbidity from cancer in the U. S. A., Monograph 29, U. S. Department of Health, Education, and Welfare, Public Health Service, 1955, Washington, D. C.

74. Hoster, H. A.: A distribution study of Hodgkin's disease in the U. S. A., *Ohio J. Sc.* **44**: 245, 1944.
75. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's disease. General considerations, *New England J. Med.* **230**: 1, 1944.
76. Shimkin, M. B., Oppermann, K. C., Bostick, W. L., and Low-Beer, B. V. A.: Hodgkin's disease: an analysis of frequency, distribution, and mortality at the University of California Hospital, 1914-1951, *Ann. Int. Med.* **42**: 136, 1955.
77. Shimkin, M. B.: Hodgkin's disease mortality in the United States 1921-1951; race, sex and age distribution; comparison with leukemia, *Blood* **10**: 1214, 1955.
78. Elsner, K. L.: An unusual case of swelling of the liver and spleen with high continuous fever, *New York M. J.* **94**: 584, 1911.
79. Diamond, H. D.: The results of therapy in Hodgkin's disease, *Ann. New York Acad. Sc.* **73**: 357, 1958.
80. Finkbeiner, J. A., Craver, L. F., and Diamond, H. D.: Prognostic signs in Hodgkin's disease, *J. A. M. A.* **156**: 472, 1954.
81. Peters, V.: A study of survivals in Hodgkin's disease treated radiologically, *Am. J. Roentgenol.* **63**: 299, 1950.
82. Peters, V.: A study of Hodgkin's disease treated by irradiation, *Am. J. Roentgenol.* **79**: 114, 1958.
83. Rosenberg, S. A., Diamond, H. D., and Craver, L. F.: Lymphosarcoma: a clinical review of 1269 cases, to be published.
84. Murray, G. R.: Hodgkin's disease, in Allbutt's System of medicine, Vol. 5, 1897, The Macmillan Company, New York, pp. 573-596, cited by Hoster et al.<sup>25</sup>
85. Street, W. W., and Allen, E. G.: Leukemia occurring in man and wife, *New York State J. Med.* **50**: 1621, 1950.
86. Gross, L.: Is cancer a communicable disease?, *Cancer Research* **4**: 293, 1944.
87. Hill, A. B.: Principles of medical statistics, 6th Ed., 1955, Oxford University Press, New York.
88. Beebe, G. W.: Expected incidence of certain neoplastic diseases in veterans, National Research Council Memorandum, issued March, 1957.
89. Anderson, R. C.: Familial leukemia. A report of leukemia in five siblings, with a brief review of the genetic aspects of the disease, *Am. J. Dis. Child.* **81**: 313, 1951.
90. Anderson, R. C., and Hezmann, H. W.: Leukemia in twin children, *J. A. M. A.* **158**: 652, 1955.
91. Ardashnikov, S. N.: Lymphatic reactions among relatives of leukaemic patients, *Brit. M. J.* **2**: 995, 1947.
92. Dameshek, W., Savitt, H. A., and Arbor, B.: Chronic lymphatic leukemia in twin brothers aged fifty-six, *J. A. M. A.* **92**: 1348, 1929.
93. Hornbaker, J. H.: Chronic leukemia in three sisters, *Am. J. M. Sc.* **203**: 322, 1942.
94. Meikle, R. W.: Two varieties of leukemia in one family, *Brit. M. J.* **2**: 468, 1944.
95. Reilly, E. B., Rapaport, S. I., Karr, N. W., Mills, H., and Carpenter, G. E.: Familial chronic lymphatic leukemia, *Arch. Int. Med.* **90**: 87, 1952.
96. Stewart, F. W.: Occupational and post-traumatic cancer, *Bull. New York Acad. Med.* **23**: 145, 1947.
97. Razis, D. V.: Unpublished data.
98. Gross, L.: The vertical epidemic of mammary carcinoma in mice. The possible implications for the problem of cancer in general, *Surg., Gynec. and Obst.* **88**: 295, 1949.
99. Levitan, R., Razis, D. V., Diamond, H. D., and Craver, L. F.: ABO blood groups in Hodgkin's disease, *Acta Hemat.* **22**: 12, 1959.

## EFFECTS OF LONG-TERM ESTROGEN THERAPY ON SERUM CHOLESTEROL AND PHOSPHO- LIPIDS IN MEN WITH MYOCARDIAL INFARCTION\*†

By JESSIE MARMORSTON, M.D., FREDERICK J. MOORE, M.D., OSCAR  
MAGIDSON, M.D., OLIVER KUZMA, M.D., and JACK J.  
LEWIS, M.D., *Los Angeles, California*

It has been well established<sup>1-8</sup> that administration of estrogen to men or women with myocardial infarction tends to raise the serum phospholipids and to lower the serum cholesterol and the cholesterol/phospholipid (C/P) ratio. In a recent communication<sup>9</sup> we noted that prolonged administration of ethinyl estradiol to postmenopausal women with myocardial infarction resulted in changes in these serum lipids, chiefly in those in whom the levels were initially abnormal. Thus estrogen therapy in effect tended to bring these serum lipids to "normal" levels.

We wish to report here the effects upon cholesterol and phospholipids of long-term estrogen therapy, using clinically well tolerated dosages, in men with coronary artery disease.

### MATERIAL AND METHODS

Four randomized groups of men have been studied; an untreated control group, and three groups treated with ethinyl estradiol, Manvene and Premarin. The entire series includes 106 individuals, of whom 96 were studied for more than 90 days, and 42 for more than one year.

*Clinical material* was drawn from the Los Angeles County Hospital and the Cedars of Lebanon Hospital. Of the total of 106 patients, all but six had sustained at least one frank myocardial infarction. These six, having clinical and electrocardiographic evidence of coronary artery disease, lacked the criteria for diagnosis of infarction. From the outset of this study, in

\* Received for publication February 25, 1959.

Read at the Regional Meeting of The American College of Physicians, Palm Springs, California, February 7-8, 1959.

From the Departments of Medicine and Public Health, University of Southern California School of Medicine, the Los Angeles County Hospital and the Cedars of Lebanon Hospital.

† Aided by grants from the Albert and Mary Lasker Foundation, and grants H-2198, H-2199 and H-2701 from the National Heart Institute.

We are indebted to Dr. Kenneth Ericson, of Organon, Inc., for supplies of Lynoral (ethinyl estradiol), to Dr. Irwin C. Winter, of G. D. Searle and Co., for Manvene (SC 6924, 3 methoxy-16 $\alpha$ -methyl-1,3,5(10)-estriene-16 $\beta$ ,17 $\beta$ -diol), and to Dr. John J. Jewell, of the Ayerst Laboratories, for Premarin (mixed conjugated equine estrogens NNR), used in these studies.

Requests for reprints should be addressed to Jessie Marmorston, M.D., 613 North Canon Drive, Beverly Hills, California.

September, 1956, efforts were made to refer all male myocardial infarction patients discharged from the two hospitals to the corresponding cardiac research clinics staffed entirely by physicians regularly participating in this study. Each patient was given a complete medical and diagnostic study in the clinic. Those accepted for this study showed unequivocal evidence of coronary artery disease, were ambulatory and able to attend the research clinic regularly, were coöperative and willing to take estrogen therapy should it be prescribed, and had no contraindication to such therapy, had no requirement for therapy with other hormones (except individuals with diabetes or myxedema), and had no concurrent illness considered to be a threat to survival. Ages of the patients reported here range from 35 to 83 years.

Patients accepted for study were allocated to a treatment or control group by the statistical office, using randomized methods. Initially, assignment was to either the ethinyl estradiol treatment or the untreated control group. After several months, Manvene was added to the randomized allocations. In April, 1957, the treatments were further increased to include a group randomly allocated to Premarin. Patients were seen at approximately three-week intervals and at each clinic visit were given the precise number of pills required for estrogen therapy at the prescribed dose until the next scheduled visit. No dietary lipid modifications were medically advised in any of the patients.

*The dosage of estrogen* used was the largest amount that was easily tolerated by the individual patient. In each patient, therefore, the initial dosage was minimal, being increased thereafter until evidence of feminization was observed. If this was quite tolerable to the patient, he might be held on that dose; otherwise, dosage was decreased to the point of acceptability. Approximately 80% of the estrogen-treated men showed a degree of breast tenderness, or other evidences of feminization, and most of the remaining 20% had been under therapy for only limited periods of time. These "side-effects" will be reported elsewhere in detail. In five patients, treatment was interrupted for more than a month, and in these individuals we have disregarded lipid data following the interruption of therapy.

Since most of the information presented here is with respect to therapy for 90 days or longer, we show in table 1 the range, arithmetic average and median for the highest dosage and for the lowest dosage employed with each medication beyond 90 days of therapy. In all cases, therapy was uninterrupted, and the estrogen was administered daily in oral doses. Approximately three quarters of the patients treated for more than 90 days with ethinyl estradiol were carried on doses ranging from 0.02 to 0.30 mg. daily; of those treated with Manvene, on doses ranging from 15 to 40 mg. daily; and of those treated with Premarin, on doses ranging from 1.25 to 3.75 mg. daily.

*Serum cholesterol* was determined by the method of Pearson et al.,<sup>10</sup> using alcohol-acetone extracts of the serum. *Lipid phosphorus* was estimated by the procedure of Lowry et al.<sup>11</sup> All patients included in this report had had lipid determinations prior to the commencement of therapy (or allocation to the untreated group), and one or more determinations thereafter. Levels during the first three weeks of therapy have been disregarded. The longest period of therapy was 20 months.

Study of the distributions of cholesterol, phospholipids and the C/P ratio indicated the desirability of making a logarithmic transformation of the data to reduce skewness and improve normalcy. All means reported

TABLE 1  
Daily Oral Dose of Estrogen Administered 90 or More Days  
after the Start of Therapy  
(Dosage varied from time to time according to tolerance of the individual patient.  
All amounts are milligrams per day.)

	Ethinyl Estradiol	Manvene	Premarin
Minimal Dose			
Range	0.010 to 0.400	5 to 80	0.625 to 10.0
Average	0.082	22.7	3.0
Median	0.050	20	2.5
Maximal Dose			
Range	0.020 to 1.000	10 to 100	1.25 to 10.0
Average	0.245	40.7	3.9
Median	0.150	30	2.5

here are geometric means. All regressions were calculated as linear on the exponential scale.

### RESULTS

Figure 1A shows the effects on serum cholesterol of estrogen administered for various periods of time. The abscissa represents pretreatment cholesterol level, and the ordinate the level observed during therapy for the indicated period of time. The regression of treatment level on pretreatment level is shown for each period, the curves being drawn over the range of pretreatment cholesterol actually observed. In addition, a broken line represents the locus of points having identical values before and during therapy. Thus, all points falling below the broken line indicate a lower level of cholesterol under therapy than before, while those above this line indicate a rise in level under therapy. The numbers of patients entering the regressions are for period I (21 to 89 days), 53 individuals; II (90 to 179 days), 48 individuals; III (180 to 364 days), 50 individuals; and IV (12 to 20 months), 24 individuals.

From figure 1A it may be seen that the results in periods II, III and IV, i.e., periods greater than 90 days, were essentially identical. With treatment for less than 90 days, the changes in serum cholesterol were some-

what less striking. Similar observations were made with respect to the cholesterol/phospholipid (C/P) ratio: after 90 days of therapy with estrogen there was little difference in the various periods of treatment, while prior to 90 days, with the doses used in this study, the C/P ratio changes were less marked. Because of these observations, we have based the remainder of this communication upon the findings under treatment for 90 days or more.

Figure 1B indicates the cholesterol changes in patients treated for more than three months with ethinyl estradiol (E, 37 patients), Manvene (M, 21 patients) or Premarin (P, 10 patients), the general construction being similar to figure 1A. The differences shown in the figure are small and lack any statistical significance. Under the conditions used in this study,

### CHOLESTEROL CHANGES IN MEN TREATED

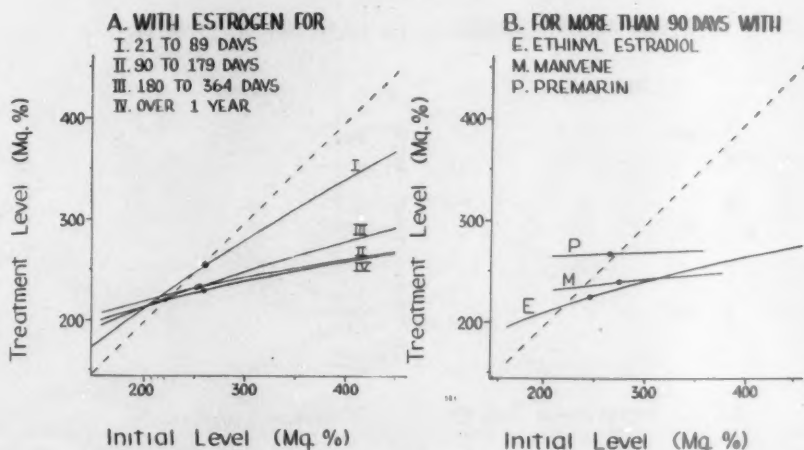


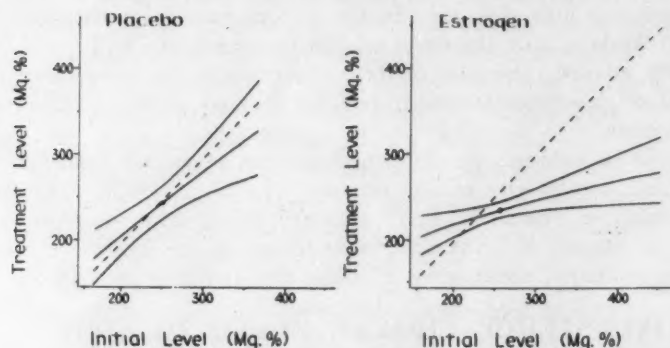
FIG. 1.

therefore, the three estrogens appeared to have similar effects upon the serum lipids.

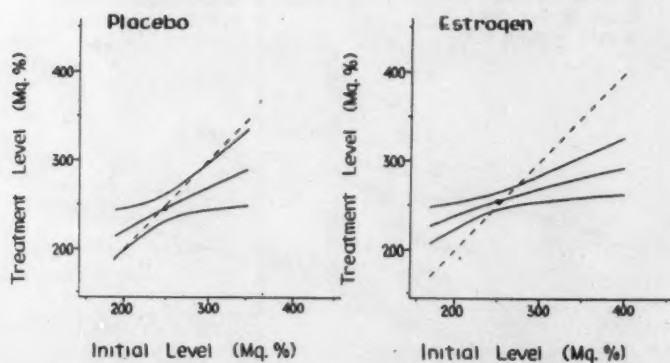
Figure 2, which is similar in general construction to figure 1, permits comparison of the lipid changes observed in the 68 estrogen-treated patients with those noted in their 28 randomized controls receiving no estrogen, all data being based on time periods greater than three months. Results are shown for cholesterol, phospholipids and the C/P ratio. In each graph a broken line is shown which represents an identity of pretreatment and treatment levels, and a regression curve representing the level observed during therapy as a function of the initial level. Also shown are the 95% confidence limits of each regression curve.

Tests of significance were carried out with respect to the difference

### CHOLESTEROL CHANGES IN MEN TREATED WITH:



### PHOSPHOLIPID CHANGES IN MEN TREATED WITH:



### C/P RATIO CHANGES IN MEN TREATED WITH:

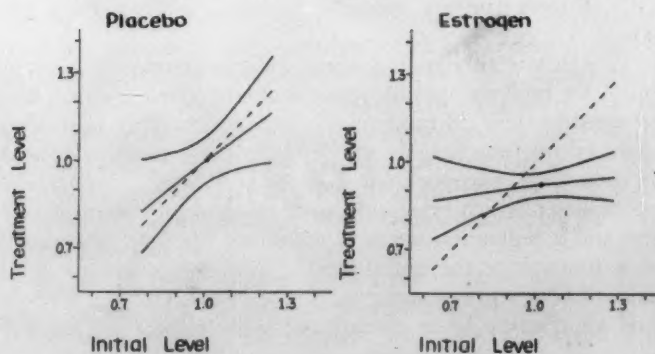


FIG. 2.

between each regression shown in figure 2 and the identity line. In the untreated controls the *p* values for this difference were 0.3, 0.02, and 0.4 for cholesterol, phospholipids and the C/P ratio, respectively. Thus, in the absence of estrogen therapy, there was no significant tendency for cholesterol or the C/P ratio to change with the passage of time, while with phospholipids there was a modest but significant tendency for initially high levels to fall and for initially low levels to rise. In the estrogen-treated patients, the corresponding *p* values were < 0.001, < 0.001, and 0.01, respectively.

TABLE 2

Changes in Serum Lipids after 90 or More Days of Therapy in Cases Divided According to Whether the Pretreatment Level Was "Low" or "High"  
(Percentage change is taken as per cent of initial level.)

	Pretreatment Mean (A)	Treatment Mean (B)	% Change	<i>p</i> value for:	
				A-B	C-D
Cholesterol					
Initial level under 250 mg. %					
14 Untreated controls	210.5	210.7	+0.1% (C)	.9	.7
28 Treated patients	214.5	221.3	+3.2% (D)	.4	
Initial level 250 mg. % or more					
14 Untreated controls	296.1	285.8	-3.5% (C)	.5	.05
40 Treated patients	287.1	245.6	-14.5% (D)	.001	
Phospholipids					
Initial level under 250 mg. %					
18 Untreated controls	223.8	230.3	+2.9% (C)	.6	.1
38 Treated patients	219.3	246.9	+12.6% (D)	.001	
Initial level 250 mg. % or more					
10 Untreated controls	295.8	274.6	-7.2% (C)	.1	.6
30 Treated patients	295.4	265.7	-10.1% (D)	.01	
Cholesterol/Phospholipid Ratio					
Initial level under 1.0					
12 Untreated controls	.900	.904	+0.5% (C)	.9	.9
26 Treated patients	.893	.890	-0.3% (D)	.9	
Initial level 1.0 or more					
16 Untreated controls	1.101	1.080	-1.9% (C)	.7	.01
42 Treated patients	1.014	.944	-14.6% (D)	.001	

It is evident, therefore, that in the treated patients there was a highly significant tendency toward normal levels: the initially high levels tended to fall and the initially low levels to remain low or even to rise under therapy with estrogen.

Tests of significance were also carried out between the regression found in the treated patients and that found in the untreated controls. This difference was statistically significant for cholesterol and the C/P ratio (*p* = 0.05 and 0.01, respectively), but lacked significance in the case of phospholipids (*p* = 0.4). In the case of cholesterol and the C/P ratio, therefore, the

changes observed under estrogen therapy may be attributed to the treatment per se. While inspection of figure 2 suggests that this may also be true with the phospholipid changes, lack of statistical significance between treated and control groups leaves this in doubt.

Examination of the raw data suggested grouping the patients according to whether their initial level was low or high, and then noting the lipid changes occurring in each of these groupings. Arbitrary dividing points were taken as 250 mg.% for cholesterol and phospholipids, and 1.0 for the C/P ratio, levels of these magnitudes or greater being termed "high." In the case of patients with initially low cholesterol levels, seven of 14 controls

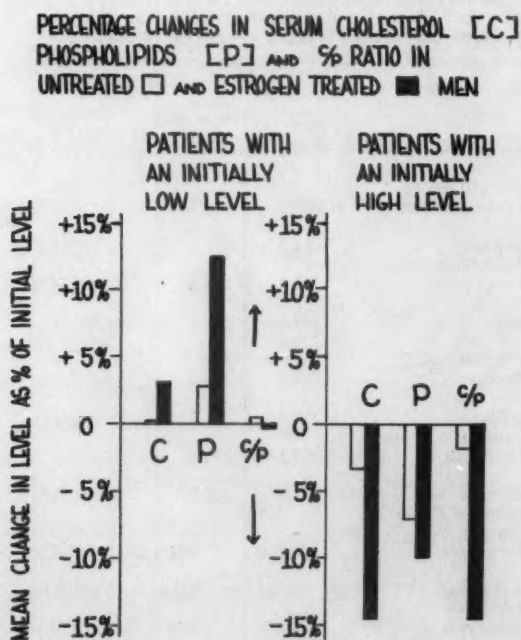


FIG. 3.

and 13 of 28 estrogen-treated patients showed a rise; while in those with initially high levels of cholesterol, seven of 14 controls and 31 of 40 treated patients showed a fall. With initially low phospholipids, 10 of 18 controls and 30 of 38 treated patients showed a rise; while with initially high phospholipids, seven of 10 controls and 19 of 30 treated patients showed a fall in level. When the C/P ratio was initially low, it rose in seven of 12 controls and in 13 of 26 estrogen-treated patients; when the ratio was initially high, it fell in 11 of 16 controls and in 34 of 42 treated patients. The mean change in level may be expressed as a percentage of the pretreatment level, as indicated in figure 3 and table 2. It is seen that significant

changes under estrogen therapy are limited to patients in whom the pre-treatment levels were elevated.

Estrogen treatment was stopped in a few patients. In two patients who had been under Manvene therapy for four and 10 months, respectively, and in four treated with ethinyl estradiol for seven, seven, seven and nine months, respectively, treatment was stopped for a variety of reasons and the patients were again seen after lapses of three, three, two, three, three and seven months, respectively. The mean pretreatment cholesterol level in these six patients was 259 mg.%; before discontinuation of treatment it had fallen to 221 mg.%; and after two to seven months untreated thereafter it had returned to 257 mg.%. Phospholipids were initially 247, rose under therapy to 276, and then returned to the original level of 247 mg.% after estrogen was discontinued. The initial C/P ratio of 1.05 fell to 0.80 during treatment and returned to 1.04 after cessation of treatment. These observations strengthen the likelihood that the phospholipid as well as the cholesterol and C/P ratio changes observed above are attributable to the estrogen therapy per se.

#### DISCUSSION

These findings indicate that significant alterations in serum cholesterol and the C/P ratio are induced and maintained in men receiving estrogen for long periods of time (from three to 20 months). It is important to note that the dosage of estrogen was generally at or near the maximum that was well tolerated by the individual patient. Most of the patients under estrogen therapy did show some evidences of feminization, and the data presented here fail to indicate whether still smaller doses would or would not have had similar effects upon the serum lipids. In women, however, we have observed substantial lipid changes under dosages that caused few or no "estrogen effects," such as bleeding or tenderness of the breast.<sup>9</sup> It therefore seems quite possible that these serum lipid changes could be induced in men with doses that fail entirely to cause reduced libido or potency, testicular changes or gynecomastia. Studies directed toward this point appear to be desirable.

The general nature of the lipid changes observed in men resembles those we previously reported in women. Thus, elevated levels tend to fall under estrogen therapy, while initially low levels tend to remain the same or even to rise. The effect is therefore toward a "normalization" of the serum lipids, and the changes observed depend to large extent upon the pre-treatment status. One inescapable consequence of this is that the change observed in the men of a series as a whole must reflect the composition of the particular sample studied: if many of its individuals had initially low levels, then little or no change might be expected in the average of the group under therapy. This point will deserve particular attention if studies are made comparing the effects of estrogen administration in normal young adults and in patients with myocardial infarction.

It is important to note that the untreated controls showed no significant alterations in either cholesterol or the C/P ratio with time (up to 20 months of observation), and that the treated patients differed significantly from the randomized controls. The serum phospholipids did tend to change in the untreated controls, the low levels tending to rise somewhat and the high levels to fall. The explanation for this change in the untreated controls remains uncertain, but it might represent sampling of a measurement where short-term fluctuation within individuals composes a substantial proportion of the total error among individuals. In the treated patients the phospholipid changes are similar in kind and amount to those found in cholesterol, and considerably greater than the phospholipid changes noted in the controls. It therefore seems quite possible that they are real and valid, but it must be emphasized that the phospholipid changes lacked statistical significance compared with the untreated controls.

The findings with Manvene, a new synthetic estrogen with relatively low estrogenic potency and relatively high lipid activity, are consistent with the findings of Cohen, Higano and Robinson.<sup>8</sup> However, in our series, where patients were randomized among the treatments, and the dose of each estrogen was pushed toward the limit of the patient's ready acceptance of continued therapy, the effects of Manvene, ethinyl estradiol and Premarin were not distinguishable. It should be noted that these studies were not designed to titrate quantitatively the effects of various dosages upon either the lipids or the "side-effects," so that no quantitatively precise conclusions concerning relative potency can be drawn from the present data. It may only be said that the three estrogens, given in doses that were roughly comparable with regard to side-effects, appeared to be very similar in their effects upon the serum lipids studied.

#### CONCLUSIONS

Determinations of serum cholesterol and phospholipids were made before and at intervals during treatment with placebo, ethinyl estradiol, Premarin or Manvene in 106 men with coronary artery disease. Estrogen dosage approximated the limit of ready acceptance of the medication by the individual patient.

After 90 days of therapy the effects of estrogen on the serum lipids appeared to be maximal, and tended neither to increase nor to decrease thereafter. The effects of ethinyl estradiol, Manvene and Premarin appeared to be very similar.

Under estrogen therapy, initially high levels of cholesterol and the C/P ratio tended to fall markedly, while initially low levels tended to remain low or even to rise. These changes differed significantly from those observed in the untreated controls. Changes similar in kind and amount in the phospholipids under estrogen therapy may be real, but they failed to attain statistical significance in comparison with the untreated controls.

These observations of an essentially "normalizing" effect of estrogen therapy on the serum lipids confirm in male subjects similar findings previously reported in postmenopausal females.

#### ACKNOWLEDGMENTS

We are grateful to Dr. Harry Sobel and Dr. Olive Hoffman, who made important contributions to early phases of the work.

Clinicians participating in these studies were Dr. Ralph Alexander, Dr. Jacob Bernstein, Dr. Irving Gordon, Dr. William Grant, Dr. Fletcher McBroom, Dr. Joseph Walker and Dr. Albert White. Laboratory determinations were made under the direction of Dr. John W. Mehl, Dr. Ross Jacobs and Dr. Sara M. Meyers.

#### SUMMARY IN INTERLINGUA

Altre autores ha establite que therapia a estrogeno tende a reducir le cholesterol del sero e a augmentar le phospholipidos del sero, con le effecto de un reduction del proportion cholesterol: phospholipido. Nos ha previeamente reportate que le perdurative therapia a estrogeno in micrissime doses exerce iste mesme effectos a grados maximal in feminas postmenopausal. Tamen, iste alterationes esseva observate principalmente in patientes in qui le valores constatate ante le tractamento habeva essite anormal. Assi, alte nivellos de cholesterol manifestava le tendentia de descender durante que normal o basse valores remaneva stabile o tendeva a montar. Ergo, estrogeno pareva exercer un effecto "normalisatori" super le lipidos seral in feminas postmenopausal.

Le presente studio extende iste observationes a homines con infarcimento myocardial. Le hormon—in le forma de Lynoral, Premarina, o Manvena—esseva administrate a 106 homines con clar signos clinic e electrocardiographic de infarcimento myocardial. Le dose initial—usate un vice per die—esseva basse. In le curso de septimanas o menses le dose esseva augmentate per micre accrescimentos usque minimal alterationes mammari esseva notate. Un dosage de mantenentia esseva establite, le qual esseva acceptabile al patiente individual como tractamento a longe vista. Le nivellos seral de cholesterol e de phospholipidos esseva determinate ante le tractamento e a varie tempores subsequente. Le plus longe periodo de observation esseva 20 menses. Simile studios in un serie de subjectos de controlo, qui esseva seligite al hasardo e qui recipeva nulle estrogeno, non reflecteva ulla significative alterationes del valores de lipido seral in le curso del tempore.

Le homines tractate con estrogeno exhibiva alterationes de lipido simile a illos previeamente reportate in feminas postmenopausal. Post circa tres menses de tractamento con micre, ben-tolerate doses, le mesme effecto "normalisatori" del hormon super le lipidos esseva evidente. Le tres preparatos de estrogeno usate manifestava iste effecto in le mesme maniera. Le alterationes inducite in le lipidos del sero per iste micre e ben-tolerate doses administrate durante prolongate periodos de tempore esseva tanto grande como illos reportate per altere autores post le uso de grande doses que causava marcate grados de gynecomastia, perdita de libido, e atrophie testicular. Per consequente, il pare integremente possibile (ben que il ha non ancora essite provate) que extrememente micre doses que causa nulle effecto clinic del toto ha nonobstante le capacitate de "normalisar" le lipidos del sero.

#### BIBLIOGRAPHY

1. Eilert, M. L.: Effects of estrogens upon partition of serum lipids in female patients, *Am. Heart J.* 38: 472, 1949.
2. Stamler, J., Pick, R., and Katz, L. N.: Experiences in assessing estrogen antiatherogenesis in chick, rabbit and man, *Ann. New York Acad. Sc.* 64: 596-619, 1956.

3. Russ, E. M., Eder, H. A., and Barr, D. P.: Influence of gonadal hormones on protein-lipid relationship in human plasma, *Am. J. Med.* **19**: 4-24, 1955.
4. Steiner, A., Payson, H., and Kendall, F. H.: Effects of estrogenic hormones on serum lipids in patients with coronary arteriosclerosis, *Circulation* **11**: 784-788, 1955.
5. Oliver, M. F., and Boyd, G. S.: Influence of sex hormones on circulating lipids and lipoproteins in coronary sclerosis, *Circulation* **13**: 82-91, 1956.
6. Robinson, R. W., Higano, N., Cohen, W. D., Sniffen, R. C., and Sherer, J. W., Jr.: Effects of estrogen therapy on hormonal functions and serum lipids in men with coronary atherosclerosis, *Circulation* **14**: 365, 1956.
7. Eilert, H. L.: Effect of estrogens on partition of serum lipids in female patients, *Metabolism* **2**: 137-145, 1953.
8. Cohen, W. D., Higano, N., and Robinson, R. W.: Serum lipid and estrogenic effects of Manvene, a new estrogen analogue, *Circulation* **17**: 1035-1040, 1958.
9. Marmorston, J., Magidson, O., Lewis, J. J., Mehl, J., Moore, F. J., and Bernstein, J.: Effect of small doses of estrogen on serum lipids in female patients with myocardial infarction, *New England J. Med.* **258**: 583-586, 1958.
10. Pearson, S., Stern, S., and McGavack, T. H.: Rapid, accurate method for determination of total cholesterol in serum, *Anal. Chem.* **25**: 813, 1953.
11. Lowry, O. H., Roberts, N. R., Leiner, K. Y., Wu, Mei-Ling, and Farr, A. L.: Quantitative histochemistry of brain; chemical methods, *J. Biol. Chem.* **207**: 1-17, 1954.

## USE OF TRIMETHIDINIUM METHOSULFATE (A NEW GANGLIONIC BLOCKING AGENT) IN THE TREATMENT OF HYPERTENSION\*†‡

By NEMAT O. BORHANI, M.D., *Baltimore, Maryland*

TRIMETHIDINIUM methosulfate is an asymmetric bisquaternary amine, possessing ganglionic blocking properties but demonstrating, in addition, a central component of antihypertensive activity.<sup>1</sup> The pharmacology of trimethidinium methosulfate has been studied by Klupp<sup>2</sup> and by Eckfeld et al.,<sup>3</sup> and its structural formula is shown in figure 1.

The antihypertensive action of this compound has been studied by O'Malley et al. It has been claimed that trimethidinium methosulfate has "hypotensive potency in excess of any quaternized ganglioplegic agents presently in use."<sup>4</sup> Furthermore, it has been observed that the ganglionic blockade produced by trimethidinium methosulfate does not necessarily parallel its hypotensive effects. In an attempt to study the relationship between ganglionic blockade and hypotensive action of this compound, Hosko and his associates studied the effects of the drug on anesthetized cats and dogs.<sup>6</sup> By using three different preparations—nictitating membrane, central stimulation and total cross circulation—these investigators observed that it is possible to produce an almost complete blockade of the superior cervical ganglion with trimethidinium methosulfate "without appreciably affecting the systemic blood pressure." However, when this compound had access only to the head of the animal by means of total cross circulation preparation, the systemic blood pressure exhibited a hypotensive response after "a latent period." It has been postulated that, although the initial hypotensive effect of this drug involves "ganglionic blockade," evidenced by relaxation produced in the nictitating membrane of intact unanesthetized cats, there is a more important component of activity in some "form of centric depression." This has led some investigators to postulate a dual mechanism of action for trimethidinium methosulfate. Therefore, the hypotensive effect of this drug and its mechanism of action are based on (a) ganglionic blockade, and (b) central effect. Both oral and parenteral administration of trimethidinium methosulfate produces hypotensive action, characterized by prompt onset and prolonged duration of action.

\* Received for publication April 30, 1959.

From the Hypertension Clinic, Department of Medicine, The Johns Hopkins Hospital, Baltimore, Maryland.

† Trimethidinium methosulfate (Ostensin, Wyeth), used in this study, was supplied by Wyeth Laboratories, Philadelphia, Pennsylvania.

‡ This study was supported in part by grant HT-5082 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

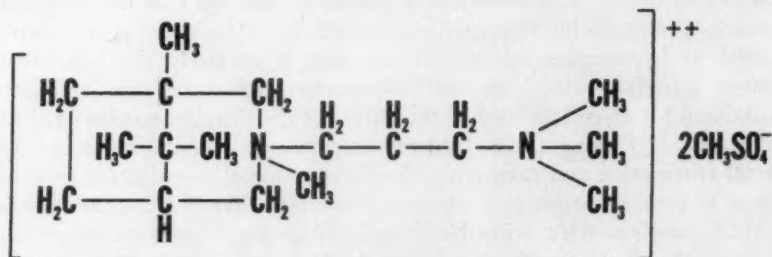
Requests for reprints should be addressed to Nemat O. Borhani, M.D., Hypertension Clinic, Department of Medicine, The Johns Hopkins Hospital, Baltimore 5, Maryland.

In animal experiments it has also been shown that duration of action of this compound is most prolonged, and that the drug has a wide margin of safety, with death resulting from respiratory depression and arrest at doses many times the therapeutic level.

It is the purpose of this report to present the therapeutic results observed after the oral administration of trimethidinium methosulfate to a group of hypertensive patients.

#### METHODS AND MATERIALS

Of a group of 45 patients receiving trimethidinium methosulfate, 30 have received the drug for a sufficient time for an opinion to be formulated on the results obtained. The remaining 15 have received the drug for less than three months and are therefore not included in this report. All participants in this study were selected from a group of patients with severe hypertensive cardiovascular disease who previously had been on one of the ganglionic blocking drugs presently in use, in combination with other anti-



d-[N-methyl-N-( $\gamma$ -trimethylammoniumpropyl)]-1-methyl-8,8-dimethyl-3-azabicyclo [3.2.1] octane dimethosulfate

FIG. 1. Trimethidinium methosulfate.

hypertensive medications, including chlorothiazide. In all patients the previous regimen of therapy (i.e., chlorothiazide and mecamlamine [Inversine], or chlorothiazide and chlorisondamine [Ecolid], etc.) was withheld, and the oral administration of trimethidinium methosulfate at a dose level ranging from 80 to 240 mg. per day was begun. All patients received the drug twice a day, during which time they received no other medication except digitalis preparations when indicated.

The patients were seen in the clinic at two- or three-week intervals. At each clinic visit a complete physical examination was performed and the blood pressure was recorded in recumbent position at 0 time (start of the examination), five-minute and 10-minute intervals. At the same session the standing blood pressure was recorded two minutes after the patient assumed the upright position. With a special check sheet, similar to the one described previously,<sup>12</sup> each physician obtained details of possible side-effects (i.e., dryness of the mouth, constipation, urinary symptoms, dizziness, etc.).

None of the patients included in this series was judged to have "malignant"

nant" hypertension from the level of diastolic blood pressure and the presence of papilledema. However, all of them had severe "benign" hypertension, with diastolic pressures around or over 120 mm. Hg. The etiology of hypertension was varied; a number with preëxisting renal disease were included.

The serum urea nitrogen was determined on all patients at regular intervals, and other laboratory studies were performed when indicated. All

TABLE I  
The Effect of Oral Administration of Trimethidinium Methosulfate on 30  
Hypertensive Patients (Blood Pressure Recorded in  
Recumbent Position)

No.	Initials	Mean Systolic Blood Pressure			Mean Diastolic Blood Pressure		
		Before Therapy	After Therapy	Difference	Before Therapy	After Therapy	Difference
1	A. J.	245.5	214.4	-31.1*	154.7	144.4	-10.3
2	B. N.	185.5	204.6	+19.1*	124	129.6	+ 5.6
3	B. M.	260	245.5	-14.6	135.7	126	- 9.7
4	B. M.	225.6	218.2	- 7.4	130.1	130.1	—
5	C. E.	232.8	242.8	+10	115.7	117.1	+ 1.4
6	C. A.	239.1	242.9	+ 3.8	155.5	155.2	- .3
7	C. E.	195.5	173.2	-22.3	121.2	109.8	-11.4
8	D. F.	226.6	186.6	-40	130	116.6	-13.4
9	F. P.	207.1	192.8	-14.3	129.3	106.9	-22.4
10	F. R.	230	206.6	-23.4	130	132.6	+ 2.6
11	F. B.	188.3	233.6	+45.3	111.6	130.7	+19.1
12	G. R.	227.5	223.3	- 4.2	147.5	136.6	-10.9
13	H. N.	216.6	187.2	-29.4	124.1	115	- 9.1
14	H. A.	195.5	254.2	+58.7	122.7	153.5	+30.8
15	H. C.	271.2	263.7	- 7.5	150.4	153.3	+ 2.9
16	I. S.	213.6	216.6	+ 3	146.3	144.6	- 1.7
17	J. L.	248.6	238.4	-10.2	136.6	127.6	- 9
18	L. S.	183.1	158.8	-24.3	121.8	108.8	-13
19	M. M.	190.2	218	+27.8	106.8	127.8	+21
20	M. V.	236	206	-30	134	118	-16
21	P. H.	186.1	211.6	+25.5	116.1	121.6	+ 5.5
22	R. J.	189.3	170	-19.3	127.5	122.1	- 5.4
23	S. W.	240	208	-32	140	140	—
24	S. J.	210.4	189.8	-20.6	132.8	125.8	- 7
25	S. S.	242.4	258.5	+16.1	141.1	149.1	+ 8
26	T. P.	249.2	246.2	- 3	143.7	139.2	- 4.5
27	T. O.	219.2	202.7	-16.5	127.8	122.2	- 5.6
28	W. J.	208.0	188.6	-20.2	136	127.3	- 8.7
29	W. C.	180	220	+40	235	152.5	+17.5
30	W. E.	218	195	-23	124	113.3	-10.7

\* (-) Fall in blood pressure.

(+) Rise in blood pressure.

of the patients were informed of the nature of the new drug, and were told to watch for the possible by-effects. They were instructed to report to the clinic should any severe side-effects develop. The dose adjustment was done entirely at the time of visit to the clinic. None of the patients took his blood pressure at home.

Because of a preponderance of Negro patients, it was not possible to draw conclusions regarding racial differences in therapeutic results.

In regard to the results summarized in tables 1 and 2, the "before therapy" blood pressure was taken as the mean of all the readings over the period of three to four months prior to the administration of this drug. Similarly, the "after therapy" blood pressure was taken as the mean of all the blood pressure readings in the three- to four-month period during which the drug was administered. On each patient an equal number of blood pressure readings both before and after therapy was used to determine the

TABLE 2  
The Effect of Oral Administration of Trimethidinium Methosulfate on 30  
Hypertensive Patients (Blood Pressure Recorded in  
Standing Position)

No.	Initials	Mean Systolic Blood Pressure			Mean Diastolic Blood Pressure		
		Before Therapy	After Therapy	Difference	Before Therapy	After Therapy	Difference
1	A. J.	235	173.5	-16.5*	150	136.8	-13.2
2	B. N.	176.6	196.6	+20 *	131.6	145	+13.4
3	B. M.	236	232.5	- 3.5	139	122.5	-16.5
4	B. M.	204.8	196.5	- 8.3	132	122.2	- 9.8
5	C. E.	220	240	+20	115	117.5	+ 2.5
6	C. A.	212.5	230	+17.5	154	148	- 6
7	C. E.	180	173.4	- 6.6	120	111.6	- 8.4
8	D. F.	226.6	186.6	-40	130	116.6	-13.4
9	F. P.	215	191.3	-23.7	135	110	-25
10	F. R.	220	200	-20	130	134	+ 4
11	F. B.	130	207.5	+77.5	95	121.2	+26.2
12	G. R.	195	180	-15	135	127.5	- 7.5
13	H. N.	207.5	182.5	-25	130	120	-10
14	H. A.	170	238.3	+68.3	120	145	+25
15	H. C.	260	260	—	140	153.7	+13.7
16	I. S.	209	205	- 4	144	150	+ 6
17	J. L.	226.6	186.3	-40.3	130	116.6	-13.4
18	L. S.	180	156.2	-23.8	110	107.5	- 2.5
19	M. M.	180	212.5	+32.5	110	127.5	+17.5
20	M. V.	240	180	-60	135	120	-15
21	P. H.	173.3	200	+26.7	117	120	+ 3
22	R. J.	172.5	170	- 2.5	135	120	-15
23	S. W.	240	160	-80	140	121.2	-18.8
24	S. J.	180	171	- 9	123	118	- 5
25	S. S.	236.6	252.6	+16	140.3	153.3	+13
26	T. P.	226.6	196	-30.6	146.6	116.6	-30
27	T. O.	212.5	196.6	-15.9	127.5	121.6	- 5.9
28	W. J.	178	174	- 4	130	134	+ 4
29	W. C.	155	186.6	+31.6	125	140	+15
30	W. E.	250	165	-85	135	114	-21

\* (-) Fall in blood pressure.

(+) Rise in blood pressure.

mean. The difference in mean systolic and mean diastolic blood pressure was determined on each occasion, and the statistical analysis was performed on a "pairing design."

#### RESULTS

The therapeutic effects of trimethidinium methosulfate on systolic and diastolic blood pressure of the 30 patients studied are summarized in tables 1

TABLE 3

Statistical Analysis of the Effect of Trimethidinium Methosulfate (Ostensin) on Systolic and Diastolic Blood Pressure of 30 Hypertensive Patients in Recumbent Position

	Systolic Blood Pressure	Diastolic Blood Pressure
Mean blood pressure difference after Ostensin..	13.1	5.68
Standard error of the mean difference.....	3.98	1.94
t.....	3.29**	2.9*

\*\* p &lt; 0.005.

\* p &lt; 0.01.

and 2. Although some of the patients did not respond to the administration of the drug, on the average there was a fall in both systolic and diastolic blood pressure. The statistical analysis of the therapeutic effect of trimethidinium methosulfate on all the patients receiving the drug is shown in tables 3 and 4 for blood pressure fall in recumbent and upright position, respectively.

In the recumbent position there was an average systolic blood pressure fall of  $13.1 \pm 3.98$ ,\* and an average diastolic blood pressure fall of  $5.63 \pm 1.94$ .\*

In the upright position the average systolic pressure fall was  $18.75 \pm 6.1$ ,\* and the average diastolic fall was  $7.88 \pm 2.3$ .\* These results, as is shown in tables 3 and 4, were statistically significant at a probability level of less than 0.005 ( $p < 0.005$ ).

It became obvious that, as in the use of any ganglionic blocking agent, frequent, often minor alterations in the dose level are necessary to control side-effects. Intelligent coöperation on the part of the patients was found to facilitate control of treatment, and, by contrast, in an unintelligent patient control was more difficult and less satisfactory. There was considerable individual variation in tolerance to the drug, as reflected in the range of dosage employed (between 80 and 240 mg. per day).

One patient not included in this series developed profound hypotension after receiving 80 mg. a day of trimethidinium methosulfate for four days.

TABLE 4

Statistical Analysis of the Effect of Trimethidinium Methosulfate (Ostensin) on Systolic and Diastolic Blood Pressure of 30 Hypertensive Patients in Standing Position

	Systolic Blood Pressure	Diastolic Blood Pressure
Mean blood pressure difference after Ostensin..	18.75	7.88
Standard error of the mean difference.....	6.1	2.3
t.....	3.07**	3.42**

\*\* p &lt; 0.005.

\* Standard error of the mean difference.

It was subsequently discovered that, contrary to specific instructions, the patient had continued to take chlorothiazide. The severe "hypotensive reaction" was probably the result of the well known potentiation of the ganglionic blockade by chlorothiazide. It has been postulated, however, that this patient may have been very sensitive to trimethidinium methosulfate, and, indeed, we have observed such a sensitivity in our clinical trial of this drug. This period of sensitivity has also been reported by others.<sup>1</sup>

We have also noticed a period of relative tolerance to this drug following the initial administration. One of our patients (L. S.) did not respond to the therapy (80 mg. a day) for a period of from five to six weeks, and then suddenly developed symptoms of "postural hypotension." There was a good fall in both systolic and diastolic blood pressure. The dose was reduced to 60 mg. per day and the response to therapy was satisfactory. She is receiving 60 mg. a day of the drug at the present time and her blood pressure is approximately normal.

#### SIDE-EFFECTS

Like any other ganglionic blockade, the administration of trimethidinium methosulfate produced some side-effects. The side-effects were mainly those related to parasympathetic blockade and, in order of frequency, were as follows:

1. Dryness of the mouth.
2. Constipation.
3. Paralysis of accommodation (blurred vision).
4. Generalized weakness.
5. Postural hypotension.
6. Occasional impotence.

Although we found trimethidinium methosulfate a very potent ganglionic blocking agent, we did not encounter the abovementioned side-effects to a severe degree. These complications were either of mild to moderate degree, or disappeared after the oral administration of 5 to 10 mg. of pilocarpine. However, in some of our patients (usually the patients who did not respond to this kind of therapy), one or a combination of these clinically disturbing side-effects was very severe. In these patients the drug was being administered in very high daily doses at the time the disturbing side-effects occurred. In some patients this drug proved to be very unpredictable, evoking no response at a certain dose and then producing side-effects as soon as the daily dose was increased slightly. These individuals may fall into the category of sensitive patients,<sup>1</sup> and they might have developed severe side-effects even if kept at the same dose level.

As is evident from a comparison of tables 3 and 4, and of great interest, the patients who responded to this therapeutic trial showed relatively

little postural hypotension. This in itself may suggest a possible central activity of trimethidinium methosulfate.

### DISCUSSION

Within the last few years, numerous pharmacologic compounds have been developed for the treatment of hypertension and hypertensive cardiovascular diseases. Among these compounds the autonomic ganglion-blocking drugs have been proved to be most potent and effective in reducing the arterial blood pressure, and therefore to be the treatment of choice in most cases of severe hypertension.

The gradually increasing tolerance to ganglionic blocking drugs requires an increase in the daily dose which, in turn, will produce more of the well known, unpleasant side-effects. Some investigators advise strongly against the use of ganglionic blocking agents in patients who have severe renal dysfunctions. On the other hand, the severe complications usually accompanying the high blood pressure and the arteriolar deterioration seen in untreated hypertensive patients<sup>11</sup> make it mandatory to lower the blood pressure in such patients by the most effective means. In this respect, there is no doubt that most of the ganglionic blocking agents presently in use are potent hypotensive agents and good therapeutic tools.

Among all the quaternary ammonium bases, the preparations which can be administered orally and which have a good absorption rate from the gastrointestinal tract seem to be the most beneficial. In this category the development of chlorisondamine (Ecolid) and mecamlamine (Inversine)—which have been shown to have good absorption on oral administration and a longer duration of action in both animals and humans—was promising. However, during the years these compounds have been in clinical use it has been found that the side-effects are similar to those found with hexamethonium and other ganglionic blocking drugs, in both degree and kind. In a comparison study, Sears et al.<sup>12</sup> found that the side-effects produced by the administration of mecamlamine were more pronounced than with pentolinium, and that constipation manifested during the course of therapy was disproportionately severe with mecamlamine, and sometimes led to paralytic ileus. Paralytic ileus due to mecamlamine, presenting as a surgical emergency, has also been reported.<sup>7</sup> Furthermore, in addition to the side-effects common to all ganglionic blocking agents, mecamlamine was found to possess two other effects, namely, the development of a "coarse tremor" and the "lack of well being."<sup>9, 12, 10</sup>

Another approach has been made to this problem with the development of an asymmetric bisquaternary compound, d-[N-methyl-N-(8 trimethyl ammonium-propyl)]-1-methyl-8, 8 dimethyl-3-azabicyclo (3-2-1) octane dimethosulfate, manufactured by Wyeth Laboratories under the trade name of Ostensin, with the structural formula shown in figure 1.

According to the pharmacologic and clinical investigations, Ostensin is a typical ganglionic blocking agent. Klupp<sup>2</sup> reported that this compound was effective in lowering the blood pressure of anesthetized animals (dogs, cats, rabbits and rats) at a dose of 100 gamma/Kg. of body weight, and that a dose of 200 gamma/Kg. was effective in maintaining the lowered blood pressure for from six to 10 hours in anesthetized as well as unanesthetized animals.

Trimethidinium methosulfate blocks the transmission of stimuli in the superior cervical ganglia without altering postganglionic excitability. As a result, hypotension is noted following blocking of the ganglia which lasts for about six to eight hours after a single oral dose. The ganglion blockade can be demonstrated by the duration of nictitating membrane paralysis in nonanesthetized animals. As with all other ganglionic blocking agents, in addition to the sympathetic ganglia, the parasympathetic ganglia are blocked by this compound, which explains, in most part, the occurrence of side-effects.

This agent is effective, either orally or parenterally, in the lowering of blood pressure, and is reported to exceed in intensity and duration of action other commonly used ganglionic blocking agents. The acute hemodynamic effects of trimethidinium methosulfate after a single intravenous injection have been reported to be like those of other ganglionic blocking agents, but the late, prolonged depressor action has been found to be unusual.<sup>14</sup> The effect on systolic blood pressure is more pronounced than the effect on diastolic blood pressure (tables 3 and 4).

In our experience, trimethidinium methosulfate has proved to be a potent ganglionic blocking agent in most hypertensive patients. It is, however, unpredictable, and should be used with great caution. This drug has a prompt and prolonged vasodepressor activity upon oral administration. The dosage should be adjusted according to the individual's response, varying from 80 to 200 mg. a day. The drug should be administered on an empty stomach, and not oftener than twice a day.

#### SUMMARY

1. The therapeutic effects of trimethidinium methosulfate (Ostensin, Wyeth) in 30 hypertensive patients are reported.
2. This drug is an asymmetric bisquaternary ammonium compound, absorbable from the gastrointestinal tract. The hypotensive effect of the drug and its mechanism of action are based on (a) ganglionic blockade, and (b) central effect.
3. The duration of action of this compound upon the oral administration is prolonged. The drug need not be used oftener than twice a day.
4. The side-effects are usually of mild to moderate degree, and may include dryness of the mouth, constipation, blurred vision and some degree of postural hypotension. The central nervous system manifestations and

the severe gastrointestinal complications sometimes seen with the use of other ganglionic blocking agents did not occur in this clinical trial.

5. Should long experience with trimethidinium methosulfate confirm this observation, the drug will have merit over other ganglion-blocking agents presently in use.

#### ACKNOWLEDGMENTS

The author wishes to express his sincere gratitude to Dr. K. A. Manley, Dr. A. P. Skyring, Dr. V. Sadarananda, Dr. D. P. Evans, Dr. K. S. Suh, Dr. J. T. Leeming and others working in the Hypertension Clinic. Without their help this study would have been impossible.

#### SUMMARIO IN INTERLINGUA

Methosulfato de trimethidinium, (Ostensina; Wyeth) es un asymmetric amina bisquaternari que possede proprietates de blocage ganglionic e un componente central de activitate antihypertensive. Le droga ha un large margine de securitate. In experimentos animal, doses multe vices plus forte que le nivello therapeutic esseva requirite pro causar le morte que occurreva allora como resultado de depression e arresto del respiration.

Iste droga ha essite administrate per via oral a 30 patientes hypertensive in un dosage de inter 80 e 240 mg per die. Omne le patientes in le studio recipeva le droga durante periodos de plus que tres consecutive menses. Le patientes esseva examine al Clinica pro Hypertension a intervallos de duo a tres septimanas. A omne iste ocasiones un complete examine physic esseva effectuate, e le tension del sanguine esseva registrate in decubito dorsal al tempores zero (comenciamento del examine), cinque minutas, e 10 minutas. Le tension sanguinee in stato erecte esseva mesurate duo minutas post que le patiente habeva prendite iste position. Le nitrogeno de urea sereal esseva determinate in omne le patientes a intervallos regular. Altere studios laboratorial esseva effectuate quando tales esseva indicate. Le patientes recipeva explicationes relative al natura del droga e le instruction de vigilar pro possibile effectos lateral e de notificar le medico in caso del disveloppamento de effectos adverse. Le dosage del droga esseva adjustate al tempore del visitas al clinica.

Le valor medie de omne le lecturas del tension de sanguine durante un periodo de tres a quatro menses ante le administration de methosulfato de trimethidinium esseva comparate con le valor medie de omne le lecturas del tension de sanguine durante le periodo de tres a quatro menses quando le droga esseva administrate. Le differentia inter le tension systolic medie e le tension diastolic medie esseva determinate pro omne examine individual, e le analyse statistic esseva effectuate secundo un "schema de appareamento."

Al media, il occurreva un reduction del tension systolic e del tension diastolic. In decubito dorsal le reduction medie del tension systolic esseva  $13,1 \pm 3,98$  e le reduction medie de tension diastolic  $5,63 \pm 1,94$ . In position erecte, le reduction medie del tension systolic esseva  $18,75 \pm 6,1$ , e le reduction medie del tension diastolic esseva  $7,88 \pm 2,3$ . Iste resultados esseva statisticamente significative a un nivello de probabilitate de minus que 0,001.

Un numero del patientes experienciava siccitate del bucca, constipation, paralyse del accomodation ocular (vision obfuscate), e debilitate general. Ben que il esseva constatate que le droga es un potente agente de blocage ganglionic, le effectos lateral non esseva de grado sever.

Methosulfato de trimethidinium es un potente agente de blocage ganglionic e possede in administrationes per via oral un prompte e prolongate activitate vasopressori. Le dosage debe esser adjustate, secundo le responsa del individuo, inter

80 e 200 mg per die. Le administration debe esser effectuate a stomacho vacue e non plus frequentemente que duo vices per die.

## BIBLIOGRAPHY

1. Dunsmore, R. A., Dunsmore, L. D., Goldman, A., Elias, M., and Warner, R. S.: Treatment of ambulatory hypertensive patients with trimethidinium methosulfate, *Am. J. M. Sc.* **236**: 483, 1958.
2. Klupp, H.: Pharmacologic investigation of a new long-acting ganglionic blocking compound, *Drug Research* **7**: 123, 1957.
3. Eckfeld, D. K., Tislow, R., and Seifter, J.: Hypotensive properties of some asymmetrical bisquaternary compounds, *American Society for Pharmacology and Experimental Therapeutics*, Baltimore, September, 4-7, 1957.
4. O'Malley, W. E., Hammerli, G. W., Rice, L. M., and Geschickter, C. F.: Studies on the antihypertensive action of *N*-dimethylaminopropyl-1-methyl-8, 8-dimethyl-3- azobicyclo (3,2,1) octane dimethochloride (WY-1395), *J. Am. Pharm. A.* **47**: 263, 1958.
5. Eckfeld, D. K., Tislow, R., and Seifter, J.: Hypotensive properties of some asymmetrical bisquaternary compounds, *J. Pharmacol. and Exper. Therap.* **122**: 21A, 1958 (abstract).
6. Hosko, M. J., Townsend, P., Tislow, R., and Seifter, J.: Hypotensive and ganglionic properties of *d*-*N*-dimethylamino-propyl-1-methyl-8, 8-dimethyl-3-azabicyclo [3,2,1] octane dimethosulfate, *J. Pharmacol. and Exper. Therap.* **122**: 33A, 1958 (abstract).
7. Grant, A. P., and Boyd, J. S.: Mecamylamine ileus as a surgical emergency, *Lancet* **1**: 713, 1957.
8. Smirk, F. H.: Results of methanum treatment of hypertensive patients, *Brit. M. J.* **1**: 717, 1954.
9. Smirk, F. H., and McQueen, E. G.: Use of mecamylamine in the management of hypertension, *Brit. M. J.* **1**: 422, 1957.
10. Doyle, A. E., and Neilson, G. H.: Neuromuscular disorders in mecamylamine therapy, *Brit. M. J.* **2**: 1431, 1956.
11. Moyer, J. H., Heider, C., Perez, K., and Ford, R. V.: The effect of treatment on the vascular deterioration associated with hypertension, *Am. J. Med.* **24**: 177, 1958.
12. Lee, R. E., Seligmann, A. W., Clarck, M. A., and Borhani, N. O.: Therapeutically refractory hypertension, *Ann. Int. Med.* **49**: 1129, 1958.
13. Sears, H. T. N., Snow, P. J. D., and Houston, I. B.: Treatment of hypertension with pentolinium and mecamylamine, *Brit. M. J.* **1**: 462, 1959.
14. Kirkendall, W. M., Armstrong, M. L., Funk, D. C., and Theilen, E. O.: Acute effects of trimethidinium methosulfate (WY 1395) on blood pressure, cardiac output, renal hemodynamics and pulse rate in man, *Circulation* **18** (Part II): 743, 1958.

## NEWER PHYSIOLOGY OF ABSORPTION FROM THE INTESTINE \*

By RICHARD J. REITEMEIER, M.D., *Rochester, Minnesota*

INCREASE in knowledge of the physiology of absorption by the gastrointestinal tract has not kept pace with advances in knowledge of renal and cardiac physiology. Contributing factors that, in part, explain this lack of progress include the relative inaccessibility of the gastrointestinal tract, its considerable length, the difficulty of sampling the portal blood, and the scarcity of adequate methods for measurement of absorption. In recent years, however, new tools and technics have appeared and have stimulated new interest and efforts. An attempt has been made in this discussion to survey only a part of the considerable literature in the field of absorption and malabsorption. In our institution, investigators have been concerned with some but by no means all of the many phases of these problems.

The process of absorption has been variously defined. By some investigators, the term is used to describe the net change in amount or volume of a substance as determined by the difference between the movement out of the lumen into the blood or lymph and the movement from the blood into the lumen. Other investigators restrict the use of the term "absorption" to the unidirectional movement of a substance from the lumen into the blood.

The term "malabsorption" has been used at times to include abnormal loss of nutrients from the intestinal tract, irrespective of whether such loss had as its basis a defect in the functional integrity of the absorbing surface. Examples of such use of the term malabsorption are shown in figure 1. In all examples depicted, excessive fecal loss of one or more nutrients may occur, but the mechanisms differ from each other, and often are not associated with defects in the process of absorption as such. Inadequate mixing may occur after gastric resection because food is diverted from supplies of bile and pancreatic enzymes. Hepatobiliary or pancreatic disease may decrease the availability of these digestive substances. In diarrheal states or in the presence of fistula the transit time through the intestine may be too rapid for normal absorption to occur. Competition for essential nutrients such as vitamin B<sub>12</sub> may exist between the host and bacteria lodging in intestinal blind loops, diverticula, or zones proximal to strictures. In sprue, the absorbing ability of the intestinal mucosa is deficient. Diseases that

\* Received for publication May 16, 1959.

Presented at the Fortieth Annual Session of The American College of Physicians, Chicago, Illinois, April 22, 1959.

From the Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Requests for reprints should be addressed to Section of Publications, Mayo Clinic, Rochester, Minnesota.

interfere with the transport of absorbed substances (as Whipple's disease and intestinal lymphoma may) provide additional examples of the variability of the site of the defect or disorder responsible for loss of nutrients from the intestinal tract.

#### FAT ABSORPTION

Among the problems of intestinal absorption, the absorption of fat has commanded perhaps the greatest attention in recent years. Benson and co-workers<sup>1</sup> studied in rats the site of fat absorption in the small intestine, utilizing radioiodinated fat, and measured the radioactivity present in the

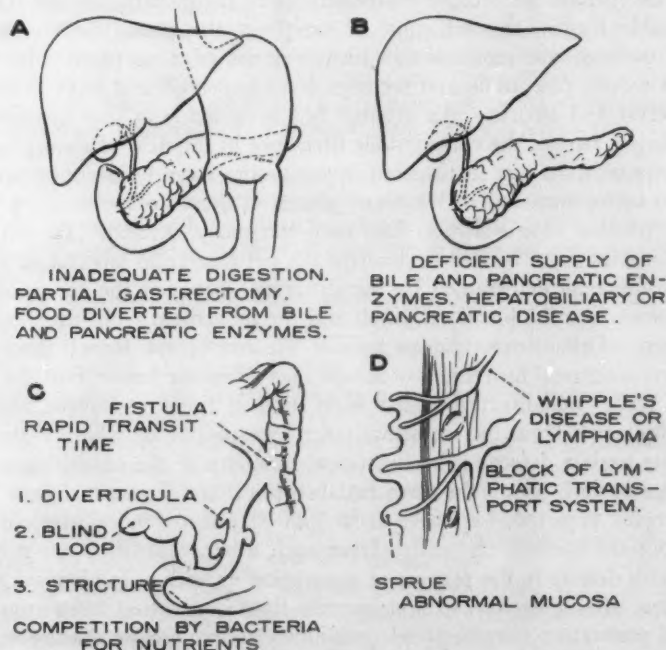


FIG. 1. Examples of possible mechanisms of excessive loss of nutrients from the gastrointestinal tract.

intestinal wall. These investigators concluded that maximal absorption of fat occurs in the third quarter of the small intestine of the rat. Borgström and associates,<sup>2</sup> however, studied absorption in humans with the use of an inert reference substance, and concluded that absorption of fat, carbohydrate and protein begins in the duodenum and is generally completed in the first 50 to 100 cm. of jejunum. These workers were able to study only the contents of the intestinal lumen.

Wherever in the small intestine may be the zone of maximal fat absorption, the lack of fat absorption has been extensively studied. Standard

laboratory methods for detection of steatorrhea have been supplemented by determination of the serum carotene level, a helpful but somewhat unreliable index of deficient fat absorption. The valuable and accurate fat balance, or intake-excretion technic, wherein chemical determination of fecal fat is carried out during usually a three-day period while the subject eats a diet of known fat composition, has been compared recently with the newer radioiodinated triolein or radioiodinated oleic acid method.

A number of investigators<sup>3-9</sup> have testified to the relative ease of using radioiodinated triolein in the study of disease states associated with steatorrhea. Generally when steatorrhea as measured by chemical determination of stool fat was marked, the  $I^{131}$  triolein content in the stools was correspondingly elevated above normal values. Some studies indicate that, by the combination of this technic with the subsequent administration of  $I^{131}$  oleic acid, a broad separation of steatorrheal states into two categories may at times be possible: If steatorrhea is due to a digestive defect, such as may be associated with pancreatic or hepatobiliary tract disease, or may follow

TABLE 1  
Combined Use of  $I^{131}$  Triolein and  $I^{131}$  Oleic Acid Absorption Tests

	$I^{131}$ Triolein (Hydrolysis Required)	$I^{131}$ Oleic Acid (Absorbed Without Change)
Digestive defect		
Gastric	Abnormal	Normal
Pancreatic		
Hepatobiliary		
Absorptive defect		
Mucosal	Abnormal	Abnormal
Lymphatic		

gastric resection, the triolein absorption may be abnormal and the oleic acid absorption normal; if an intestinal absorptive defect exists, as in sprue, the absorption of both the triglyceride and the fatty acid may be low (table 1).

Some differences of opinion have arisen as to the relative merits of the fecal and the blood determinations of radioactivity in the tagged-fat method.

As an investigative tool, iodinated fat has certain limitations and disadvantages. Beres and co-workers<sup>3</sup> noted that the technic using  $I^{131}$  triolein was not sufficiently sensitive to detect mild disturbances in pancreatic function, and in patients having steatorrhea associated with regional enteritis they found poor correlation between absorptive radioiodinated triolein blood patterns and the chemical fat balance.

Moertel and others<sup>10</sup> in our institution, in a study soon to be reported, have noted good correlation between results of the chemical fat balance and  $I^{131}$  triolein technics when the degree of steatorrhea is marked, but poor correlation when the steatorrhea, as evidenced by chemical determination, is mild or of even moderate degree. From a practical diagnostic standpoint,

it usually is only those instances of mild steatorrhea that require any type of elaborate technic, gross or microscopic inspection of the stool often sufficing in instances of marked steatorrhea.

More important limitations of the use of  $I^{131}$  as a label for triglyceride have been pointed out by Van Handel and Zilversmit.<sup>11</sup> These workers administered triglycerides together with  $I^{131}$  fat to dogs and rats. They measured the increase over the fasting levels of triglyceride as determined chemically in blood and lymph, and compared this with the specific lipid radioactivity imparted by the  $I^{131}$  fat. When such a mixture was given intravenously, clearance from the blood was found to be nearly equal for the two methods. When the mixture was given orally, however, the increase in triglycerides was disproportionately high in comparison with the amount of lipid radioactivity. Similar deficiencies of  $I^{131}$  as a fat label were demonstrated when carbon <sup>14</sup> triolein was given orally with  $I^{131}$  triolein. Proportionately, the content of carbon <sup>14</sup> triolein in the lymph was found to be essentially the same as the chemically determined triglyceride, but the  $I^{131}$  triolein activity again was decreased. The ratio of  $I^{131}$  to carbon <sup>14</sup> was found in the lymph to be four or five to 10. The investigators concluded that  $I^{131}$  triolein does not appear to give a quantitative measure of the amount of fat absorbed, whether this is due to some loss of  $I^{131}$  from the fat during absorption, or whether  $I^{131}$  triolein is absorbed at a rate different from triolein. A comparison of results from use of  $C^{14}$  oleic acid and of  $I^{131}$  oleic acid was much nearer unity, with some exceptions.

At present, it appears that the comparison of absorption of radioiodinated triglyceride with absorption of radioiodinated fatty acid in certain cases of steatorrhea in which the question of a digestive versus an absorptive defect arises is a promising use of isotopically labeled fat. For precise quantitative measurement of steatorrhea, the older fat balance method seems unequaled.

The test for urinary excretion of d-xylose<sup>12</sup> probably is a good clinical screening procedure for defective intestinal absorption.

#### VITAMIN B<sub>12</sub>

The use of radiocobalt vitamin B<sub>12</sub> has made possible the study of absorption of this vitamin in healthy subjects as well as in patients with disease states. Published work is in agreement that—whether absorption of  $Co^{60}B_{12}$  is measured by means of fecal radioactivity, the Schilling urinary excretion, or hepatic uptake methods—no absorption of the labeled-vitamin is detectable in the absence of gastric intrinsic factor, a situation that exists in patients with pernicious anemia (table 2). In certain patients whose small intestine has diverticula, strictures or blind loops, failure of absorption of radioactive B<sub>12</sub> is not improved by addition of intrinsic factor. In these instances the absorptive defect is corrected by the oral use of a tetracycline drug that is believed to change the abnormal bacterial flora existing in these segments of the intestine.<sup>13, 14</sup> In patients with sprue, the deficiency of

TABLE 2

Effect of Intrinsic Factor and Tetracycline on Absorption of Vitamin B<sub>12</sub>Co<sup>60</sup>

Disease State	Intrinsic Factor	Tetracycline
Pernicious anemia	Corrected	No change
Intestinal stricture, blind loop or diverticula	No change	Improved
Sprue	No change	No change

vitamin B<sub>12</sub> absorption is not corrected by administration of either intrinsic factor or oral tetracycline, and the absorptive defect is believed to exist within the intestinal mucosa.<sup>13, 15</sup>

Pancreatic steatorrhea has also been associated with impaired vitamin B<sub>12</sub> absorption,<sup>13</sup> and this perhaps is explained by Gräsbeck and co-workers,<sup>16</sup> who have reported enhanced B<sub>12</sub> absorption in patients with steatorrhea due to sprue when calcium lactate was administered with the vitamin. In steatorrhea, formation of insoluble calcium soaps tends to remove calcium otherwise available for absorption, and conceivably this may retard vitamin B<sub>12</sub> absorption.

Booth and Mollin<sup>17</sup> have found vitamin B<sub>12</sub> to be absorbed maximally from the middle and distal thirds of the small intestine in animals, and from a later study in man have concluded that the critical amount of bowel necessary for B<sub>12</sub> absorption is 6 to 8 feet of ileum.

#### ABSORPTION OF WATER AND ELECTROLYTES

The large volumes of fluid exchanged between intestinal lumen and blood, as measured by flux rates, and the finding that certain electrolytes such as chloride can be absorbed against large concentration gradients,<sup>18</sup>

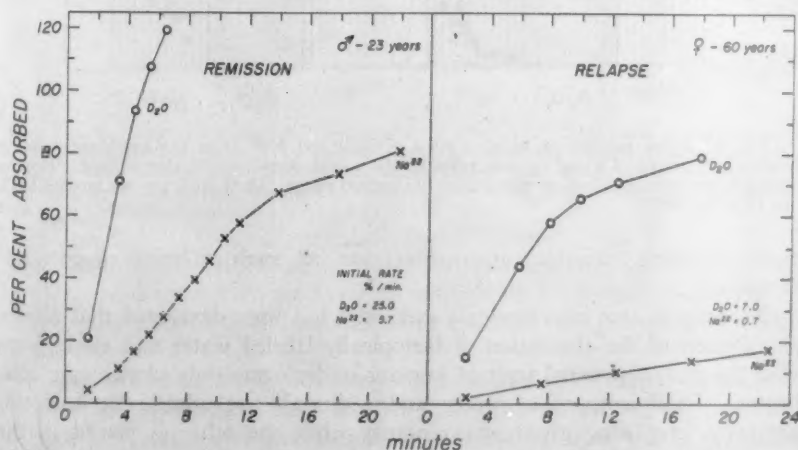


FIG. 2. Examples of rates of absorption of D<sub>2</sub>O and Na<sup>24</sup> in two patients with sprue of differing degrees of severity.

increase our respect for the absorptive ability of the intestinal mucosa. Such studies are still in their early stages at present, and much of the information already obtained has merely given rise to new questions regarding the physiology of absorption. Reference will be made here to only a part of this aspect of the process.

Ideally, the study of absorption of any substance is carried out without disturbance of the gastrointestinal tract and under physiologic conditions. The use of aspiration tubes, blocking of segments of the intestine with balloons, and construction of isolated loops of intestine have made possible

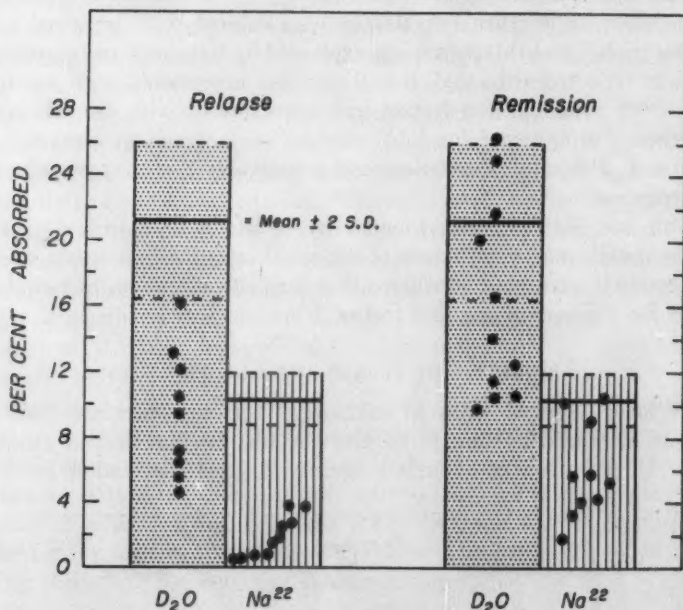


FIG. 3. Rates per minute of absorption of  $D_2O$  and  $Na^{22}$  from the small intestine in patients with sprue. During relapse, rates of absorption were considerably slowed. During remission, the rates reached or approached the normal range (16 to 26% per minute for  $D_2O$ , 8 to 12% for  $Na^{22}$ ).

studies yielding valuable information; but all such technics remain unphysiologic.

Recently in our laboratories a method<sup>19</sup> has been developed that allows quantitation of the absorption of isotopically labeled water and electrolytes from the gastrointestinal tract of humans under completely physiologic conditions. Dual isotopes of water and sodium<sup>20</sup> are administered simultaneously, one being given intravenously while the other is placed in the bowel. Determination of the concentration of the isotopes in the same samples of arterial blood then yields simultaneous rates of entry of isotope

into the blood from the intestine and disappearance of isotope from the blood into the tissues. Integration of these rates for each substance then yields the rate of absorption of the isotope. The term "absorption" here is restricted to the rate of passage of isotope from bowel into blood; net change is not measured.

In healthy subjects the mean rate of absorption of  $D_2O$  (heavy water) was found to be 21% per minute, while sodium was absorbed at a mean rate of 10% per minute.<sup>21</sup> Lee and associates<sup>22</sup> observed in healthy subjects that

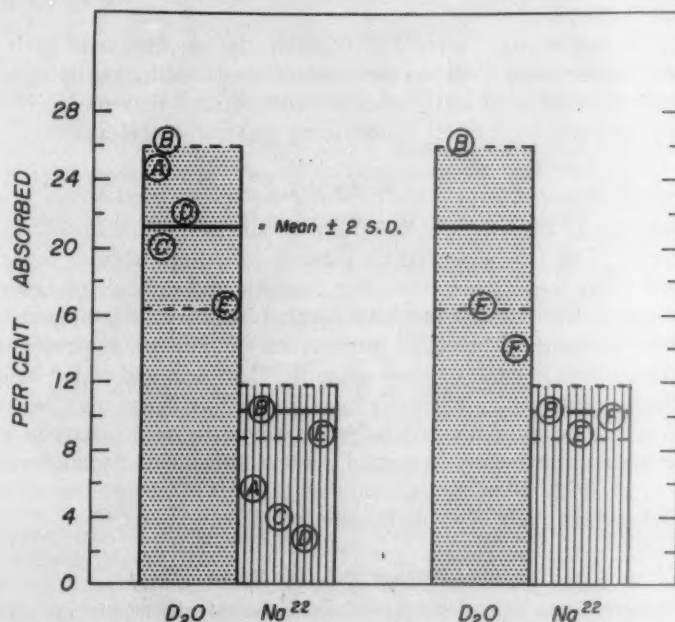


FIG. 4. Lack of correlation between rates of absorption of  $D_2O$  and of  $Na^{22}$  in patients during remissions of sprue. The pair of bars at left show the normal rates of  $D_2O$  absorption in some patients and their corresponding rates of  $Na^{22}$  absorption. The pair of bars at right show the normal rates of  $Na^{22}$  absorption in other patients and their corresponding rates of  $D_2O$  absorption.

the absorption of  $D_2O$  from the small intestine was similar when the heavy water was administered as either an isotonic or a hypotonic solution. Delayed rates of absorption occurred when the  $D_2O$  was given as a hypertonic solution.

Supplementing a previous study,<sup>23</sup> a total now of 20 fasting patients with nontropical sprue have been studied with this method. The rates of absorption of both water and sodium were found to be slower in the patients with sprue than in healthy subjects. As a rule, absorption of sodium was restricted more than was that of water (figure 2). Nine of the patients

were studied during an exacerbation of their disease, and it can be seen from figure 3 that absorption of  $D_2O$  and Na was quite markedly slowed. In 11 patients studied while in a remission of their disease, the rates of absorption of  $D_2O$  and sodium are seen to be less severely affected, although few reached the normal range. It might be anticipated that attainment of a normal rate of  $D_2O$  absorption by a patient studied while in a remission would be associated with attainment of a corresponding normal rate of sodium absorption. Figure 4 demonstrates that this correlation does not always exist.  $D_2O$  and sodium absorption appear to be governed by different mechanisms.

Higgins and others<sup>24</sup> were able to delay the absorption of both heavy water and radiosodium from the small intestine of healthy subjects by intravenous administration of methantheline bromide, and they measured simultaneously the depressant effect of this drug on small-bowel motility.

#### SUMMARY

Absorption of many substances from the small intestine is only partially understood. The forces regulating passage of materials from intestine to blood and from blood to intestine are complex and difficult to investigate. The fat balance technic has not been equaled by the radioiodinated triolein method as a means of detecting steatorrhea of mild or moderate degree. When comparison is made of absorption of  $I^{131}$  triolein and of  $I^{131}$  oleic acid, the distinction between an absorptive and a digestive defect may be possible. The use of  $Co^{60}$  vitamin  $B_{12}$  has helped to elucidate the mechanism responsible for macrocytic anemia in certain abnormalities of the small bowel. A method is available allowing quantitation of rates of absorption of isotopic water and certain electrolytes under physiologic conditions.

#### SUMMARIO IN INTERLINGUA

Le progresso de nostre cognoscentias relative al physiologia del absorption intestinal ha non essite rapide. Isto resulta in parte ab le inaccessibilitate relative del intestino, su longor, le difficultate de obtener specimenes de sanguine portal, e le paucitate de adequate methodos pro mesurar le absorption.

Le termino "malabsorption" ha essite usate pro describir un varietate de defectos de digestion, de defectos in le mixtion de nutrientes con bile e enzymas, e de defectos in le transporto de materiales a transverso le intestino si ben como de defectos absorptive a propriemente parlar. Le absorption de grassia esseva studiate recentemente per medio de trioleina a  $I^{131}$ . Iste technica pare esser digne de confidentialia solmente quando le grado del steatorrhea es marcate. Il pare que le combination de trioleina a  $I^{131}$  con acido oleic a  $I^{131}$  permette le distinction inter defectos absorptive e defectos digestive. Studios con trioleina a  $I^{131}$  in animales experimental pare indicar que iste methodo de marcation non provide un adequate quantification del grassia absorbite. Le methodo traditional del determination del balancia de grassia, in que le grassia dietari e le grassia fecal es chimicamente quantificate, remane inequalate.

Vitamina  $B_{12}$  es absorbite in le ileum. Gastric factor intrinsec es necessari pro le absorption, sed disruption del absorption de vitamina  $B_{12}$  occorre in diverticulos

intestinal, stricturas, o ansas cec. Es opinat que illo es causate in tal casos per le concurrentia del parte de bacterios que existe in tal segmentos anormal. Iste defecto es corrigite per le uso de un droga tetracyclina. In sprue, ni factor intrinsec ni tetracyclina meliora le defective absorption de vitamina B<sub>12</sub>. Il pare que illo es promovite per iones de calcium.

Un methodo pro le mesuration del intensitate absorptional de aqua pesante e de natrium isotopic ha demonstrate un defective absorption de iste isotopos in patientes con sprue in comparison con subjectos normal. A generalmente parlar, le absorption de natrium esseva retardate plus marcatamente que le absorption de aqua pesante, e ambe ille isotopos esseva absorbite minus ben in recidivas que durante periodos de remission del morbo.

#### BIBLIOGRAPHY

1. Benson, J. A., Jr., Chandler, G. N., Vansteenhuyse, F. E., and Gagnon, J. O.: Studies concerning the site of fat absorption in the small intestine of the rat, *Gastroenterology* 30: 53, 1956.
2. Borgström, B., Dahlqvist, A., Lundh, G., and Sjövall, J.: Studies of intestinal digestion and absorption in the human, *J. Clin. Investigation* 36: 1521, 1957.
3. Beres, P., Wenger, J., and Kirsner, J. B.: The use of I<sup>131</sup> triolein in the study of absorptive disorders in man, *Gastroenterology* 32: 1, 1957.
4. McKenna, R. D., Bourne, R. H., and Matzko, A.: The use of I<sup>131</sup> labeled fat in the study of fat digestion and absorption in normal individuals and in patients with diseases of fat absorption, *Gastroenterology* 32: 17, 1957.
5. Shingleton, W. W., Baylin, G. J., Isley, J. K., Sanders, A. P., and Ruffin, J. M.: The evaluation of pancreatic function by use of I<sup>131</sup> labeled fat, *Gastroenterology* 32: 28, 1957.
6. Ruffin, J. M., Keever, I. C., Cheers, C., Jr., Shingleton, W. W., Baylin, G. J., Isley, J. K., and Sanders, A. P.: Further observations on the use of I<sup>131</sup>-labeled lipids in the study of diseases of the gastrointestinal tract, *Gastroenterology* 34: 484, 1958.
7. Grossman, M. I., and Jordan, P. H., Jr.: The radio-iodinated triolein test for steatorrhea, *Gastroenterology* 34: 892, 1958.
8. Kaplan, E., Edidin, B. D., Fruin, R. C., and Baker, L. A.: Intestinal absorption of iodine<sup>131</sup>-labeled triolein and oleic acid in normal subjects and in steatorrhea, *Gastroenterology* 34: 901, 1958.
9. Berkowitz, D., Sklaroff, D., Woldow, A., Jacobs, A. G., and Likoff, W.: Blood absorptive patterns of isotopically-labeled fat and fatty acid, *Ann. Int. Med.* 50: 247, 1959.
10. Moertel, C. G., Owen, C. A., Jr., Scudamore, H. H., and Wollaeger, E. E.: Personal communication to the author.
11. Van Handel, E., and Zilversmit, D. B.: Limitation of radioiodine as a label for fat, *J. Lab. and Clin. Med.* 52: 831, 1958.
12. Benson, J. A., Jr., Culver, P. J., Ragland, S., Jones, C. M., Drummey, G. D., and Bougas, E.: The d-xylose absorption test in malabsorption syndromes, *New England J. Med.* 256: 335, 1957.
13. Halsted, J. A., Swendseid, M. E., Lewis, P. M., and Gasster, M.: Mechanisms involved in the development of vitamin B<sub>12</sub> deficiency, *Gastroenterology* 30: 21, 1956.
14. Scudamore, H. H., Hagedorn, A. B., Wollaeger, E. E., and Owen, C. A., Jr.: Diverticulosis of the small intestine and macrocytic anemia with report of two cases and studies on absorption of radioactive vitamin B<sub>12</sub>, *Gastroenterology* 34: 66, 1958.
15. Glass, G. B. J.: Intestinal absorption and hepatic uptake of vitamin B<sub>12</sub> in diseases of the gastrointestinal tract, *Gastroenterology* 30: 37, 1956.
16. Gräsbeck, R., Kantero, I., and Siurala, M.: Influence of calcium ions on vitamin B<sub>12</sub> absorption in steatorrhea and pernicious anaemia, *Lancet* 1: 234, 1959.

17. Booth, C. C., and Mollin, D. L.: The site of absorption of vitamin B<sub>12</sub> in man, *Lancet* **1**: 18, 1959.
18. Visscher, M. B., Fetcher, E. S., Jr., Carr, C. W., Gregor, H. P., Bushey, M. S., and Barker, D. E.: Isotopic tracer studies on the movement of water and ions between intestinal lumen and blood, *Am. J. Physiol.* **142**: 550, 1944.
19. Scholer, J. F., and Code, C. F.: Rate of absorption of water from stomach and small bowel of human beings, *Gastroenterology* **27**: 565, 1954.
20. Scholer, J. F., Orvis, A. L., Higgins, J. A., and Code, C. F.: Use of dual isotopes in determination of rates of absorption in intact animals, *Am. J. Physiol.* **183**: 659, 1955.
21. Reitemeier, R. J., Code, C. F., and Orvis, A. L.: Comparison of rate of absorption of labeled sodium and water from upper small intestine of healthy human beings, *J. Appl. Physiol.* **10**: 256, 1957.
22. Lee, P. R., Code, C. F., and Scholer, J. F.: The influence of varying concentrations of sodium chloride on the rate of absorption of water from the stomach and small bowel of human beings, *Gastroenterology* **29**: 1008, 1955.
23. Higgins, J. A., Lee, P. R., Scholer, J. F., Reitemeier, R. J., Code, C. F., and Wollaeger, E. E.: Absorption of water and sodium from the small intestine of patients with nontropical sprue, *J. Clin. Investigation* **36**: 265, 1957.
24. Higgins, J. A., Code, C. F., and Orvis, A. L.: The influence of motility on the rate of absorption of sodium and water from the small intestine of healthy persons, *Gastroenterology* **31**: 708, 1956.

## FACTORS CONTROLLING HEMOPOIESIS: EXPERIMENTAL OBSERVATIONS ON THEIR ROLE IN POLYCYTHEMIA VERA \*

By JAMES W. LINMAN, M.D., *Chicago, Illinois*, FRANK H. BETHELL, M.D., F.A.C.P.,† *Ann Arbor, Michigan*, and MARTHA J. LONG, M.S., *Chicago, Illinois*

It has long been evident that erythropoiesis is governed by equilibrated forces which maintain the normal erythroid steady state and determine erythropoietic responses to stimuli arising from physiologic and pathologic changes. Until recently, however, little was known concerning the manner by which erythrocytic equilibrium was maintained or restored. During the last few years, studies in many laboratories have established the existence of a humoral erythropoietic regulatory mechanism,<sup>1,2</sup> and evidence is now available which suggests that the formation of other hemic elements may be subject to similar controlling factors.

Our previous studies<sup>3-5</sup> indicate that two humoral factors exert control over erythropoiesis. A thermostable, ether-soluble agent appears to stimulate erythroblastic cellular division but does not enhance hemoglobin synthesis, which is apparently governed by a relatively thermolabile, ether-insoluble substance. The erythrocytic responses in recipient rats given unmodified active plasmas, which contain both of these humoral agents, are characterized by increases in all of the usual parameters that reflect erythropoietic activity, in addition to others such as the erythrocytic uptake of iron-59. Similar effects are exerted by the filtrates of such plasmas which have been boiled for five minutes or less, but after more prolonged boiling these same test materials fail to augment either iron-59 incorporation or the hemoglobin and hematocrit levels in recipient animals. The relative thermolability of the humoral agent responsible for the stimulus to hemoglobin synthesis has also been emphasized by others.<sup>6-8</sup>

We have, however, consistently observed a singular type of response in normal rats given multiple daily injections of the extracts of active plasmas processed by boiling for 30 minutes or more. It is characterized by erythro-

\* Received for publication July 6, 1959.

Presented at the Fortieth Annual Session of The American College of Physicians, Chicago, Illinois, April 20, 1959.

From the Department of Medicine, Northwestern University Medical School, and the Veterans Administration Research Hospital, Chicago, Illinois; and the Department of Internal Medicine and the Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Michigan.

Aided by Research Grant No. A-1991 from the National Institutes of Health, U. S. Public Health Service.

† Deceased.

Requests for reprints should be addressed to James W. Linman, M.D., Veterans Administration Research Hospital, 333 East Huron, Chicago 11, Illinois.

cytosis, due to the production of microcytes, and reticulocytosis without associated increases in hemoglobins or hematocrits. The small cells responsible for the erythrocytosis are evident on stained films and demonstrable by Price-Jones measurements. Recipients of these plasma extracts also exhibit myeloid erythrocytic hyperplasia which, together with the erythrocytosis and reticulocytosis, provides conclusive evidence of increased erythropoietic activity. Ether-soluble fractions of erythropoietically active plasmas evoke identical responses in recipient rats,<sup>4</sup> whereas the enhancing effect on iron-59 incorporation is retained in the ether-insoluble portions. After the injections of such plasma extracts are discontinued, the prompt restoration of normal erythrocyte counts coincides with the disappearance of the microcytes, and is apparently due to impaired viability of these small cells, as evidenced by their decreased osmotic resistance when determined by a direct cell enumeration technic using red cell pipets and hypotonic salt solutions as diluents.<sup>9</sup>

Increased proliferative activity of myeloid erythrocytic precursors in the absence of a comparable stimulus to hemoglobin synthesis or hemolysis would appear to be the only alternative explanation for the hematologic phenomena observed in normal rats given the thermostable or ether-soluble fractions of active plasmas. Although a compensated hemolytic state secondary to erythrocytic cytolysis with impaired viability of the resultant fragments would explain all of the findings, definite augmentation in hemoglobin production would be a prerequisite for the maintenance of normal hemoglobin and hematocrit levels. Under these circumstances, enhanced iron-59 incorporation in hemoglobin should be evident in recipient rats. Since it is not, hemolysis would seem unlikely. It may therefore be postulated that these plasma fractions exert a primary stimulatory effect on erythroblastic cellular division.

Although the erythropoietic activity of certain plasmas and sera has been assumed by many workers to be due to only one substance which stimulates hemoglobin formation, it is somewhat difficult to envision a single agent's affecting each of the multiple and seemingly diverse physiologic processes that encompass erythropoiesis. However, it is readily apparent that an increase in the number of erythrocytic precursors differentiated from the primitive myeloid reticulum cells will, if all other conditions remain normal, lead to increased hemoglobin production. We are in accord with the theory<sup>2, 10</sup> that the humoral agent, which appears to be a mucoprotein,<sup>2, 8, 11, 12</sup> exerts such an effect on the pluripotential myeloid reticulum cells. Experimental observations indicate that the time required for the maturation of erythrocytic precursors and the synthesis of hemoglobin is predetermined, perhaps by nutritional and hormonal environment, and is apparently independent of the humoral stimulus or total output by the marrow.<sup>13</sup> On the other hand, there is no compelling support for the contention that the proliferation of nucleated red cells, which is basically nuclear and occurs chiefly

by homeoplastic mitosis, and the synthesis of hemoglobin, largely a cytoplasmic function, must be responsive to a single stimulus. Examples of disparity between these aspects of erythropoiesis are evident, and the studies described above indicate that the number of cellular divisions which the erythrocytic precursors undergo during maturation is governed by a second humoral factor. The latter is resistant to prolonged boiling, is ether-soluble, and appears to be a lipid. It is proposed that these two humoral erythropoietic factors control, individually, the quantity of hemoglobin and the number of erythrocytes produced, and that their combined activities determine, in addition, the hemoglobin content and size of each erythrocyte.

Even though many questions remain unanswered, existent data justify certain conclusions. Enhanced plasma erythropoietic activity has been found in a variety of clinical and experimental situations of diverse etiologies but with some type of hypoxia in common. The precise manner by which hypoxia controls the elaboration or activation of these humoral agents is not known, but since dilution anemia is not accompanied by increased erythropoiesis,<sup>14</sup> it may be inferred that the relationship between oxygen supply and tissue metabolic requirements determines the level of plasma factor activity. This well balanced regulatory mechanism apparently comprises the primary erythropoietic stimulus, and ensures, in the presence of sufficient metabolic building blocks and an intact myeloid reticulum, an oxygen-carrying capacity of the blood commensurate with cellular needs and the production of red cells which are of an optimal size and hemoglobin content. It may be concluded with reasonable certainty that the humoral factors contribute to the maintenance of the erythroid steady state and are responsible for the accelerated erythropoiesis associated with blood loss anemia and hypoxic hypoxia. The role of these agents in anemic states due to defective erythrocytogenesis is more debatable, since an altered myeloid reticulum or certain deficiencies will preclude a normal marrow response. Studies in this field are now in progress in many laboratories, and it seems probable that some abnormality of the humoral mechanism will be found to be of pathogenetic significance in certain currently ill defined anemias.

Enhanced erythropoietic stimulatory activity is also present in the plasma of patients with polycythemia vera,<sup>15, 16</sup> and persists after normal erythroid values have been achieved by specific therapy. The erythrocytosis and reticulocytosis induced in normal rats by boiled extracts of plasmas obtained from two patients with polycythemia vera before and after treatment with P-32 are shown in figure 1. The responses in these animals were similar in all respects to those previously described in recipients of certain "anemic" or "hypoxic" plasmas, and were not associated with increased hemoglobin or hematocrit levels. Microcytes with decreased osmotic resistance were demonstrable, and myeloid erythrocytic hyperplasia was evident (figure 2) as determined by a method for femoral marrow examination previously described.<sup>17</sup> To date we have studied the plasmas from 16 patients with

active polycythemia vera and eight in therapeutic remission. Identical erythrocytic responses were induced in normal rats given multiple daily injections of the thermostable or ether-soluble fractions of each of these plasmas. Augmented amounts of the humoral agent which enhances hemoglobin synthesis are also detectable in such plasmas when tested in the unmodified state, or after boiling for less than five minutes.

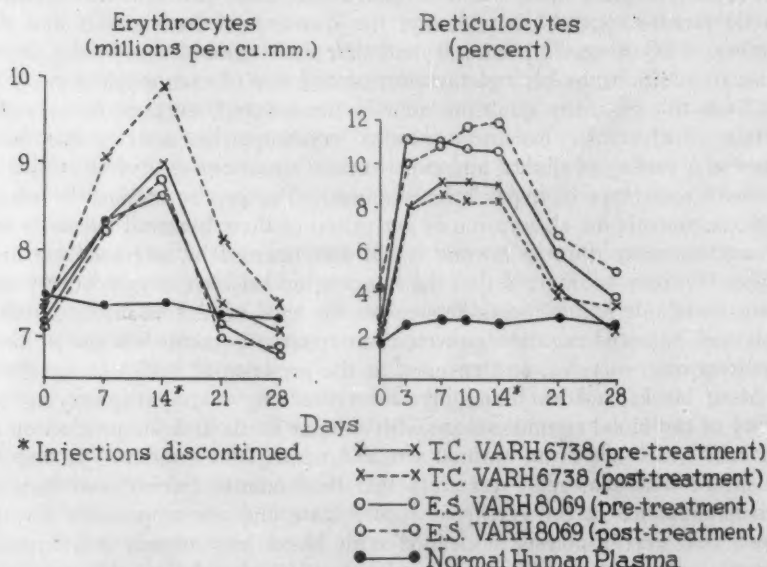


FIG. 1. Erythrocytosis and reticulocytosis in normal rats given daily subcutaneous injections (Saturdays and Sundays excepted) equivalent to 2% of their body weights of the extracts of "polycythemic" plasmas which had been processed by boiling for 30 minutes. Average counts of six animals receiving each of the above described materials. All hemoglobin determinations in these recipients were within 0.5 gm.% of their respective base line levels. The donor's erythroid values were:

	Pretreatment		Post-treatment (P-20)	
	T. C.	E. S.	T. C.	E. S.
Hemoglobin (gm. %)	19.5	18.2	14.2	15.2
Hematocrit (vol. %)	63.5	63.5	49.5	45.0
R.B.C. ( $\times 10^6$ /cu. mm.)	7.5	8.5	5.1	5.5

Since polycythemia vera was initially described by Vaquez,<sup>18</sup> in 1892 and established as a specific disease entity a few years later by Saundby and Russell<sup>19</sup> and by Osler,<sup>20</sup> its etiology has been the subject of much speculation. Although the clinical manifestations and the natural course of the disease have been clearly defined,<sup>21-23</sup> the pathogenesis remains *sub judice*. The more commonly held theories of causation are hypoxia, a hypophysial-hypothalamic abnormality, a neoplastic process, or a derangement in the normal erythropoietic regulatory mechanism. Since erythropoietic hyper-

activity is evoked by hypoxia, many attempts have been made to implicate it as a cause of polycythemia vera. However, there is no evidence of an oxygen deficit in this disorder. Arterial and marrow blood oxygen saturation is normal,<sup>21, 24, 25</sup> and pulmonary hyperoxia fails to reduce the rate of erythropoiesis.<sup>26</sup> Furthermore, the splenomegaly, leukocytosis and thrombocytosis so commonly associated with polycythemia vera indicate a pathogenetic mechanism other than simple hypoxia. Endeavors to assign the midbrain a primary role in the etiology of polycythemia vera have also been unsuccessful. The widely held concept that polycythemia vera is a neo-

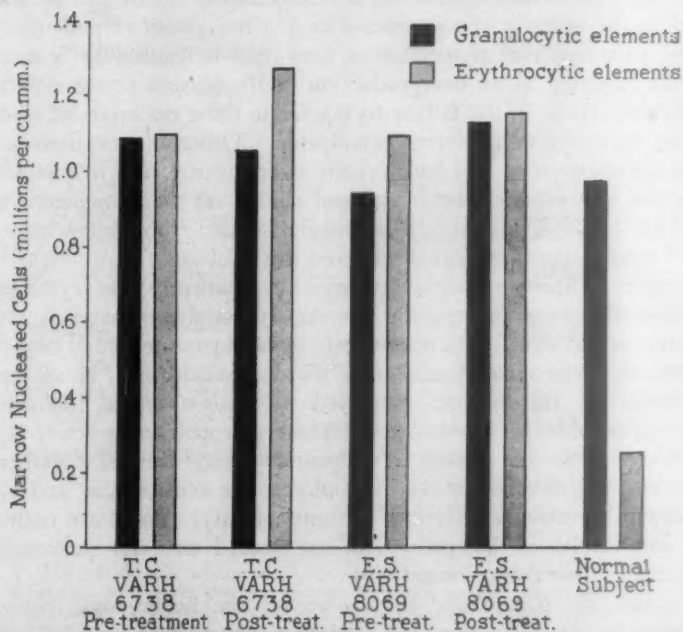


FIG. 2. Myeloid erythrocytic hyperplasia in rats injected with the "polycythemic" plasma extracts described in figure 1. Average marrow nucleated cell counts of three animals receiving each of the above described materials.

plastic disease is supported by its association with leukemia and other myeloproliferative disorders, but it fails to meet the criteria of a malignant process.

The theory that polycythemia vera may result from an abnormality in a physiologic regulatory mechanism, in the past considered by most to be speculative, is no longer without experimental support. Since the plasma factors do not appear to be a by-product of hyperactive myeloid elements,<sup>27, 28</sup> considerable significance must be attached to the presence in this disorder of enhanced humoral erythropoietic activity which persists irrespective of the institution of myelosuppressive therapy and occurs in the absence of

hypoxia, the apparent cause for such a finding in all other situations. Although increased plasma erythropoietic activity has been observed in all of the patients with polycythemia vera that we have studied so far, it should be pointed out that this has not been a consistent finding. Contopoulos and his associates<sup>10</sup> were able to demonstrate augmented activity in most but not all such plasmas tested, and Gordon<sup>2</sup> has also described negative results. It is possible that there is more than one form of this disease. However, varying degrees of increased plasma factor activity, perhaps insufficient to be detected by the relatively insensitive assay technics available, would seem to be a more plausible explanation, which is supported by the evident differences in the severity of the process in a given group of patients. It is therefore proposed that polycythemia vera may be caused by a metabolic imbalance resulting in an overproduction of the plasma erythropoietic factors, or, conversely, in the failure to inactivate these materials at rates sufficient to maintain erythrocytic equilibrium. Other observations suggest that the thrombocytosis and leukocytosis so frequently seen in this disorder may be due to a similar mechanism, and studies on the hemopoietic effects of batyl alcohol, a glyceryl ether previously isolated from yellow bone marrow,<sup>20, 20</sup> would appear to bear directly on this problem.

Recent experiments in our laboratories have confirmed the erythropoietic, thrombopoietic and granulopoietic stimulatory activity of batyl alcohol.<sup>31, 32</sup> This compound is effective in normal rats by both parenteral and oral routes, and induces erythropoietic responses which are identical in all respects demonstrable by the methods employed to those observed following the administration of boiled or ether extracts of erythropoietically active plasmas. Thrombocytosis is also evident in recipients of batyl alcohol, together with leukocytosis, due chiefly to a relative and absolute neutrophilia, and myeloid granulocytic hyperplasia. Greater amounts of batyl alcohol are required to induce granulocytosis, however, than are needed to exert detectable erythropoietic or thrombopoietic activity.

Although the physiologic significance of the hematologic phenomena ascribed to batyl alcohol is as yet conjectural, they are in accord with the thesis that all aspects of hemopoiesis may be under the influence of humoral regulatory mechanisms, and that a single substance may control the proliferative activity of all hemic elements. In addition, the chemical and physiologic attributes common to batyl alcohol and the ether-soluble, thermostable plasma erythropoietic factor suggest, logically but without proof, that these substances may be closely related. Further studies on the role of humoral factors in polycythemia vera support this concept.

We have yet to study an active plasma, regardless of the experimental or clinical conditions under which it was obtained, that has not possessed activity attributable to both humoral factors. Augmented amounts of each of these agents have been demonstrated in the plasmas of patients with polycythemia vera by *in vitro* assay technics, thereby explaining the increase

in all of their erythroid values. However, the *in vivo* effect of the factor which regulates the proliferative activity of erythrocytic precursors appears to predominate in these patients, and microcytes are present in their peripheral blood.<sup>5</sup> These cells, which are remarkably similar to those observed in normal rats given the thermostable, ether-soluble plasma erythropoietic factor, also possess decreased osmotic resistance when determined by a direct cell enumeration technic, and persist during therapeutic remission. This apparent bimodality of the erythrocyte population in patients with polycythemia vera is in agreement with the observations of others. Berlin and

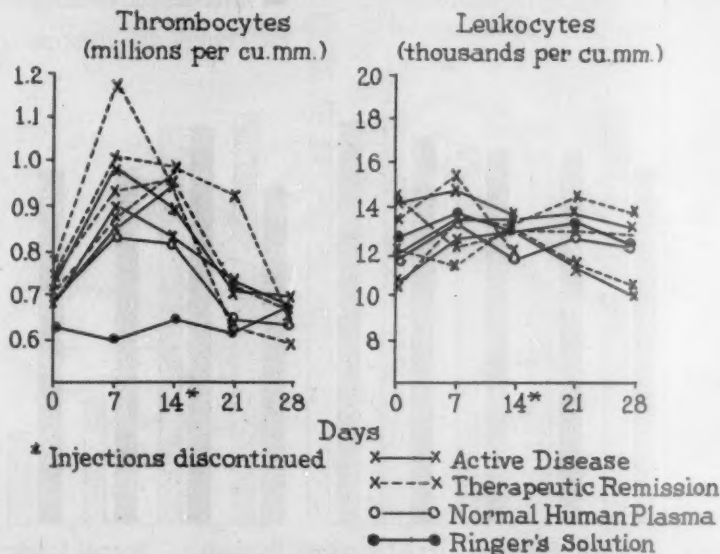


FIG. 3. Thrombocytosis without leukocytosis in normal rats given the ether-soluble fractions of plasmas from seven patients with polycythemia vera. (Three had active disease and four had normal erythroid, leukocyte and thrombocyte values subsequent to treatment with P-32.) Daily subcutaneous injections (Saturdays and Sundays excepted) were equivalent to 2% of the recipients' body weights. The normal plasma extract appeared to exert a minimal thrombopoietic effect, but was erythropoietically inactive. Average counts of six animals receiving each of the plasma extracts and a similar number injected with Ringer's solution.

his co-workers<sup>33</sup> have described studies with a carbon-14 labeled glycine technic, and concluded that the red cells of these patients can be divided into two classes, one possessing a normal survival time, the second a lifespan of only a few days. Although most descriptions of the peripheral blood in patients with polycythemia vera fail to mention any significant anisocytosis, microcytes have been noted,<sup>34</sup> and were emphasized by Price-Jones.<sup>35</sup>

These findings assume added import in view of the possible relationship of the thermostable, ether-soluble plasma erythropoietic factor to batyl alcohol, a substance which exerts a stimulatory effect on the proliferation of

all myeloid elements. Consequently, experiments were designed to test the hypothesis that the thrombocytosis and leukocytosis so commonly observed in polycythemia vera might be the result of humoral factor activity. Plasmas were obtained from three patients with active polycythemia vera and from four in therapeutic remission, and lyophilized. Prior to testing, they were extracted three times with reagent ether. The ether washings of each plasma were pooled and the ether was removed under reduced pressure. The residue was reconstituted to the original volume of the plasma with

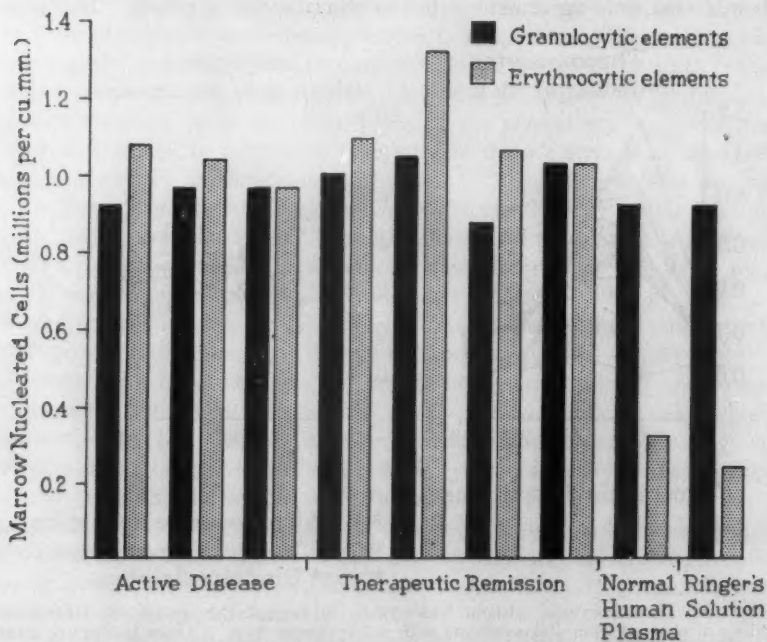


FIG. 4. Increased numbers of nucleated red cells without augmentation in granulocytic elements at the end of the injection period in the marrows of the recipients of the "polycythemic" plasma extracts which induced the thrombocytic responses depicted in figure 3. Average counts of three rats receiving each of the seven "polycythemic" plasma extracts, and similar numbers injected with a normal human plasma extract and Ringer's solution.

distilled water. The extract from each individual patient was then assayed in a group of normal rats, the animals receiving 10 daily injections equivalent to 2% of their body weight over a period of two weeks. Erythrocytic responses consisting of erythrocytosis due to the production of microcytes, reticulocytosis, and myeloid erythrocytic hyperplasia without associated increases in hemoglobins or hematocrits were observed in the recipients of each "polycythemic" plasma extract. In addition, these materials were found to exert a thrombocytosis-promoting effect in normal rats (figure 3). Although not marked, a definite increase in platelets was a consistent finding

in all animals, with a prompt return to normal after the injections were stopped. These animals failed to manifest significant leukocytosis (figure 3) or myeloid granulocytic hyperplasia (figure 4). However, increased marrow nucleated red cell counts were observed, and megakaryocytes were very numerous. The normal human plasma extract was erythropoietically inactive but did appear to contain minimal thrombopoietic activity (figure 3).

Since our studies with batyl alcohol indicated a relationship between dosage and the type of response,<sup>31, 32</sup> the above experiments were repeated

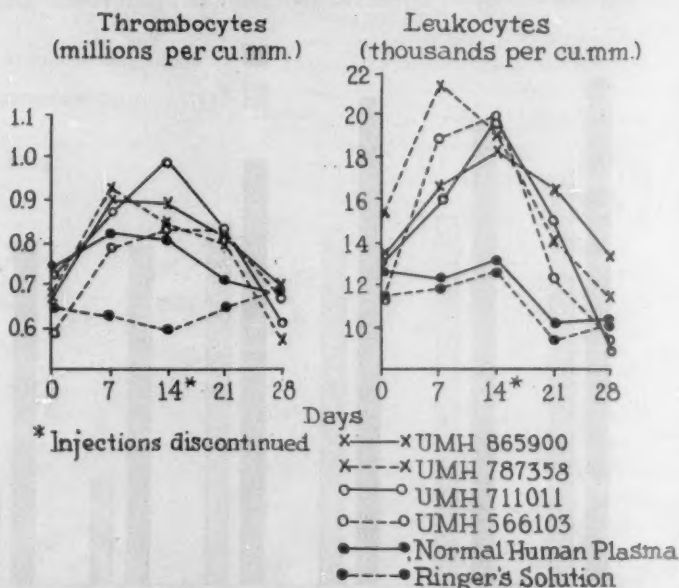


FIG. 5. Thrombocytosis and leukocytosis in normal rats given boiled extracts of plasmas from four patients with active polycythemia vera. Daily subcutaneous injections (Saturdays and Sundays excepted) were equivalent to 4 ml. of the original plasma per 100 gm. body weight. All values in those animals not killed for marrow examination returned promptly to base line levels after the injections were stopped. The leukocytosis was due chiefly to a relative and absolute neutrophilia. Average counts of four rats receiving each of the above described materials. The hematocrits and leukocyte counts of the donors are shown in figure 6. Each of these patients also had moderate to marked thrombocytosis.

to determine if larger amounts of "polycythemic" plasma extracts would induce a leukocytic response in normal rats. Plasmas from four additional patients with active polycythemia vera were used. All of these patients manifested increased erythroid values and moderate to marked thrombocytosis. Leukocytosis was present in three. The pH of each plasma was adjusted to 5.5 by the addition of 1N hydrochloric acid and processed for testing by boiling over a direct flame for 30 minutes. The coagulum was removed by filtration and the filtrate reconstituted with distilled water to

one-half the original volume of the plasma. Normal human plasma was treated in a similar manner. Each plasma extract was given to a group of normal rats in daily doses which, although calculated on the basis of 2 ml. per 100 gm. of body weight, were equivalent to twice the quantity previously used. Typical erythrocytic responses were elicited, and thrombocytosis was again observed (figure 5). Normal plasma once more appeared to possess minimal thrombopoietic activity. These recipients of greater amounts of "polycythemic" plasma extracts also manifested leukocytosis (figure 5). The latter was due chiefly to a relative and absolute neutrophilia, although

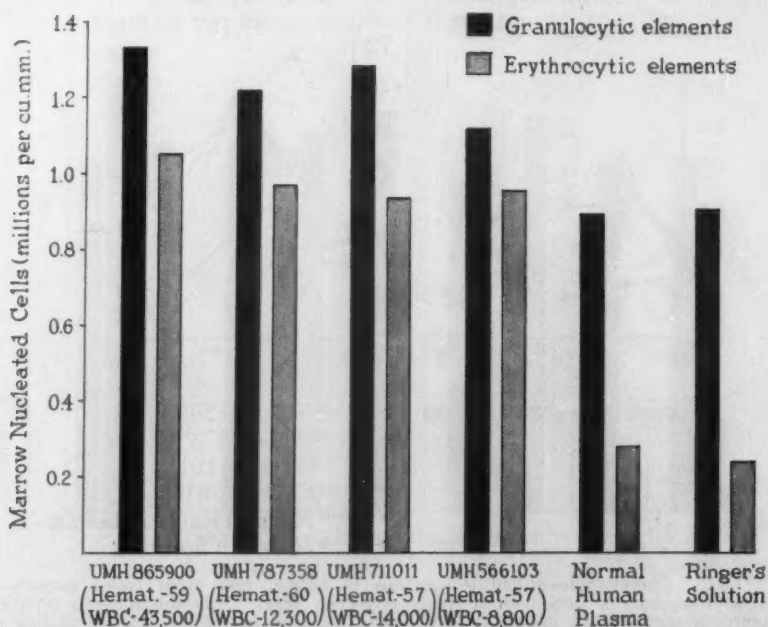


FIG. 6. Myeloid erythrocytic and granulocytic hyperplasia in rats injected with the "polycythemic" plasma extracts which induced the thrombocytosis and leukocytosis depicted in figure 5. The hematocrits and leukocyte counts of the donors are shown in parentheses. Average determinations of two rats receiving each of the above described materials.

lymphocytes, monocytes and eosinophils were slightly increased. The constancy of the leukocytosis in all animals and the rapid return to normal after the injections were stopped contribute to the significance of this finding, as do the marrow nucleated cell counts. Femoral marrow was examined in half of the rats in each group at the end of the treatment period, and both granulocytic and erythrocytic hyperplasias were demonstrated (figure 6). Megakaryocytes were also noted to be increased.

Similar studies on the plasmas from four other patients with active polycythemia vera and one with normal values subsequent to treatment with

P<sup>32</sup> have corroborated the myelopoietic effect of such materials. In addition to the usual erythrocytic response, normal rats given injections of the boiled extracts of these plasmas in daily doses equivalent to 3 or 4 ml. of the original plasma per 100 gm. of body weight developed leukocytosis and thrombocytosis (table 1), and increased numbers of both erythrocytic and granulo-

TABLE 1

Leukocytosis and Thrombocytosis in Normal Rats Injected with Boiled Extracts of Plasmas from Patients with Polycythemia Vera; Average Counts of Four Rats in Each Group Given These Materials, and of Eight Receiving the Normal Plasma Extract and Ringer's Solution

Test Materials	Daily Dose (ml./100 gm.)	Leukocytes ( $\times 10^3$ ) and Thrombocytes ( $\times 10^4$ ) per cu. mm.					
		Determination	Base Line	1 Week	2 Weeks*	3 Weeks	4 Weeks
UMH 852687 Hemat. 55 WBC 13,050 Plts. normal	4	WBC	14.1	16.2	20.4	12.8	—
		Platelets	.500	.864	.995	.745	.610
UMH 514267 Hemat. 52 WBC 10,000 Plts. increased	3	WBC	14.7	19.8	22.6	11.5	—
		Platelets	.604	.852	.893	.647	.661
UMH 811765 Hemat. 52 WBC 14,500 Plts. increased	4	WBC	13.4	15.3	17.5	13.5	—
		Platelets	.662	.929	.998	.746	.701
UMH 707644 Hemat. 47 WBC 15,250 Plts. increased	3	WBC	14.7	16.6	18.4	12.8	—
		Platelets	.528	.856	.972	.745	.694
UMH 835356 Hemat. 53 WBC 8,700 Plts. normal (3 months after Rx with P <sup>32</sup> )	3	WBC	11.2	19.1	26.2	14.0	—
		Platelets	.705	1.075	.864	.718	.725
Normal Human Plasma	4	WBC	12.7	11.5	12.9	10.9	—
		Platelets	.718	.784	.805	.718	.709
Ringer's Solution	4	WBC	12.7	12.0	11.8	10.3	—
		Platelets	.699	.700	.667	.705	.706

\* Injections discontinued.

cytic elements in their marrows (table 2). The recipients of the normal human plasma extract again manifested slight elevations in their thrombocyte counts without evidence of erythropoietic stimulation or leukocyte increases.

These observations would appear to establish beyond reasonable doubt

the presence of thrombopoietic and granulopoietic activity in the plasmas of patients with polycythemia vera. However, there apparently exist, at least in the normal rat, varying degrees of sensitivity of the different myeloid elements to the stimulus contained in these "polycythemic" plasma extracts. To elicit a detectable leukopoietic effect in recipient rats, larger doses than those which have consistently induced erythrocytosis and thrombocytosis have been needed of most but not all such plasmas tested. Although not described herein, we have observed leukocytosis in animals injected with lesser amounts of plasma extracts from three patients with active polycythemia vera. It is of interest that the leukocytic responses in other rats given twice the quantity of these same materials were numerically comparable. It should also be noted that the smallest dosage used in these experiments apparently imparted the maximal stimulus to erythropoiesis and thrombopoiesis, since the erythrocyte and thrombocyte increases were similar in all groups, regardless of the size of the daily injection. Therefore, the limitations imposed by the bio-assay technic were such that it was impossible

TABLE 2

Myeloid Erythrocytic and Granulocytic Hyperplasia in Normal Rats Injected with Boiled Extracts of Plasmas from Patients with Polycythemia Vera (See Table 1); Average Counts of Two Animals Receiving Each of These Materials, and of Four Given the Normal Plasma Extract and Ringer's Solution

Test Materials	Marrow Nucleated Cells per cu. mm.	
	Total Granulocytic	Total Erythrocytic
UMH 852687	1,300,228	1,011,585
UMH 514267	1,151,257	960,024
UMH 811765	1,286,823	989,561
UMH 707644	1,118,124	843,744
UMH 835356	1,114,934	935,450
Normal human plasma	948,427	291,229
Ringer's solution	952,658	256,185

to quantitate the hemopoietic effects of these plasmas, or to relate the type or degree of response in the rats to the magnitude of the erythrocytosis, thrombocytosis or leukocytosis in the patients. However, it may be assumed that the presence of active disease in the donors is not a prerequisite for the *in vitro* detection of a hemopoietic stimulus in their plasmas.

The demonstration of thrombopoietic and granulopoietic stimulatory activity in the thermostable, ether-soluble fractions of "polycythemic" plasmas provides direct support for the theory that all aspects of myelopoiesis are subject to humoral regulatory control, and strongly suggests that a single substance or activator-inhibitor complex may influence the formation of all hemic elements. Multiple humoral factors, each exerting control over the proliferation of a single cell type, cannot be excluded, but the thrombocytic and leukocytic stimuli in "polycythemic" plasmas have not been dissociated from the thermostable, ether-soluble plasma erythropoietic factor which has been studied. The similarities between the physiologic properties of batyl

alcohol and the thermostable, ether-soluble fractions of "polycythemic" plasmas also rule against this possibility.

It may be reasonably concluded from these observations that humoral factors are responsible for the thrombocytosis and leukocytosis associated with polycythemia vera in addition to the accelerated rate of erythropoiesis, thus strengthening the role of these agents in the pathogenesis of this disorder. The stimulus to this derangement in the humoral regulatory mechanism, however, remains unknown. Confirmation of a stimulatory effect of the thermostable, ether-soluble plasma erythropoietic factor on other hemic precursors would clarify the pathogenesis of the proliferation of myeloid elements *en masse* in certain conditions. Examples are the heretofore unexplained thrombocytosis and leukocytosis which occur after acute blood loss and in certain hemolytic states. The fact that thrombocytosis and leukocytosis do not always accompany the erythroid hyperplasia in experimental animals or human subjects with enhanced plasma erythropoietic activity from endogenous or exogenous sources does not necessarily detract from this hypothesis. The final response is undoubtedly governed by a number of variables. Moreover, the observations in recipients of batyl alcohol and "polycythemic" plasma extracts indicate varying degrees of sensitivity or responsiveness of the different myeloid elements to these particular stimuli. Therefore, the level of humoral factor activity may influence both the type and the degree of response. In this regard, the thrombocytosis and leukocytosis following acute hemorrhage are related to the rapidity and extent of the hemorrhage, and subside after restoration of erythrocytic equilibrium is under way, and when certain cardiopulmonary adjustments have relieved to some extent the tissue anemic hypoxia, and consequently the apparent stimulus to the elaboration or activation of the factor. There also exists a suggestive correlation between the severity of certain hemolytic processes and the thrombocyte and granulocyte increases that may accompany them.

The significance, if any, of the possible thrombopoietic effect of normal human plasma has not been elucidated. However, this finding is compatible with the observations of Schulman and his associates<sup>36</sup> on a child with chronic thrombocytopenia. Normal plasma has repeatedly but temporarily corrected the platelet deficiency in this patient, thus suggesting the presence in normal individuals of a plasma thrombopoietic factor. It is also of interest that concentrates of normal human plasma contain demonstrable erythropoietic activity.<sup>3</sup>

The problem of the physiologic and pathophysiologic control of hemopoiesis is a complex one that has not yet been solved. Although the entire subject needs further study before definitive conclusions can be reached, recent experimental observations are such that the primary importance of humoral regulatory mechanisms can no longer be denied.

## SUMMARY

Our studies indicate that two humoral factors exert basic regulatory control over erythropoiesis. A relatively thermolabile, ether-insoluble agent augments hemoglobin synthesis, whereas a thermostable, ether-soluble factor appears to govern the mitotic or proliferative activity of erythrocytic precursors. This humoral mechanism most likely constitutes the primary erythropoietic stimulus, and is apparently responsible for the maintenance of the normal erythroid steady state and for the accelerated erythropoiesis which accompanies hypoxic and certain types of anemic hypoxia. The presence of enhanced plasma erythropoietic activity in patients with polycythemia vera, which occurs in the absence of hypoxia and persists irrespective of the institution of specific myelosuppressive therapy, supports the thesis that the humoral factors are of etiologic importance in this disorder. The ether-soluble or thermostable fractions of plasmas from patients with polycythemia vera also possess thrombocytic and granulocytic stimulatory activity. It is suggested that batyl alcohol, a substance which also induces erythrocytosis, thrombocytosis and granulocytosis in normal rats, may be closely related to the thermostable, ether-soluble plasma factor. Although the precise significance of the hemopoietic effects of batyl alcohol and of the plasmas of patients with polycythemia vera is still speculative, these observations lend credence to the theory that all aspects of hemopoiesis are under humoral regulatory control. A single agent may affect (although not to the exclusion of other mechanisms) the formation of all hemic elements, and may explain the thrombocytosis and leukocytosis associated with such conditions as polycythemia vera, acute hemorrhage and hemolysis. Further study of the factors controlling hemopoiesis should clarify our understanding of certain currently obscure hematologic disorders and responses.

## SUMMARIO IN INTERLINGUA

Nostre studios indica que duo factores exerce un effecto regulatori super le erythropoiese. Un agente que es relativamente thermolabile e que es insolubile in ethere augmenta le synthese de hemoglobina, durante que un factor que es thermostabile e solubile in ethere pare governar le activitate proliferative del precursores erythrocytic. Iste mechanismo humoral constitue probabilissimamente le primari stimulo erythropoietic e pare esser responsabile pro le mantenentia del normal stato stabile erythroide e pro le accelerate erythropoiese que accompania hypoxia e certe typos de hypoxia anemic.

Le presentia de un intensificate activitate erythropoietic del plasma in patientes con polycythemia ver que occurre in le absentia de hypoxia e persiste sin riguardo a si o non un therapia myelosuppressive es instituite supporta le these que factores humoral es de signification etiologic in iste disordine. Usque al tempore presente nos ha studiate le plasmas de 16 patientes con active polycythemia ver e de octo patientes con polycythemia ver in remission therapeutic. In omne iste casos nos ha potite observar un augmento del activitate erythropoietic. Le thermostabile fractiones de iste plasmas—o le fractiones solubile in ethere—induceva responsas in le ratto normal le quales esseva identic in omne respectos con le responsas previeamente describite in recipientes de simile extractos ab plasmas "anemic" o "hypoxic."

Augmentate quantitates del agente humoral que promove le synthese de hemoglobina es etiam demonstrabile in tal plasmas "polycythemic" quando illos es testate in stato non modificate o post breve periodos de ebullition.

Le fractiones soluble in ethere, o le fractiones thermostabile, de plasmas ab patientes con polycythemia ver se ha etiam monstrate capace a inducer thrombocytosis o leucocytosis in rattos normal. Tamen, plus grande quantitates esseva requirite pro evocar leucocytosis in comparation con le quantitates necessari pro evocar un detegibile activitate erythropoietic o thrombopoietic. Le leucocytosis, causate principalmente per un relative e absolute neutrophilia, esseva accompagnate de myeloide hyperplasia granulocytic. Iste studios indica que le thrombocytosis e leucocytosis que es si communmente associate con polycythemia ver es possiblement etiam le resultado de un activitate de factores humoral. A causa de similaritates in lor proprietates chimic e physiologic, le these es proponite que alcohol batylic—un substantia que ha essite isolate ab jalne medulla ossee—es strictemente relationate con le thermostabile, ethero-solubile factor plasmatic.

Ben que le signification physiologic del effectos hematopoietic de alcohol batylic e del plasma de patientes con polycythemia ver ha non ancora essite elucidate, le phenomenos observate se trova apparentemente de accordo con le theoria que omne aspectos del hematopoiese es regulate per factores humoral. Il pare possibile que un sol agente o un sol complexo de activator e inhibitor affice—ben que non necessarimente al exclusion de altere mecanismos—le formation de omne le elementos hemic e pote explicar le thrombocytosis e le leucocytosis que es associate con conditiones como polycythemia ver, hemorrhagia acute, e hemolyse. On pote expectar que studios additional del factores regulatori in le hematopoiese va clarificar nostre comprension de certe disordines e responsas hematologic que al tempore presente es ancora obscur.

#### BIBLIOGRAPHY

1. Sacks, M. S.: Erythropoietin, Editorial, *Ann. Int. Med.* **48**: 207-212, 1958.
2. Gordon, A. S.: Hemopoietine, *Physiol. Rev.* **39**: 1-40, 1959.
3. Bethell, F. H., Linman, J. W., and Korst, D. R.: Erythropoietic activity of "anemic" and "polycythemic" plasmas, *Tr. A. Am. Physicians* **70**: 297-304, 1957.
4. Linman, J. W., Bethell, F. H., and Long, M. J.: Studies on the nature of the plasma erythropoietic factor(s), *J. Lab. and Clin. Med.* **51**: 8-16, 1958.
5. Linman, J. W., Korst, D. R., and Bethell, F. H.: Some observations on the stimulation of erythropoiesis by humoral factors, *Ann. New York Acad. Sc.* **77**: 638-649, 1959.
6. Stohlman, F., Jr., and Brecher, G.: Humoral regulation of erythropoiesis. IV. Relative heat stability of erythropoietin, *Proc. Soc. Exper. Biol. and Med.* **95**: 797-800, 1957.
7. Gurney, C. W., Jacobson, L. O., and Goldwasser, E.: The physiologic and clinical significance of erythropoietin, *Ann. Int. Med.* **49**: 363-370, 1958.
8. Lowy, P. H., Keighley, G., Borsook, H., and Graybiel, A.: On the erythropoietic principle in the blood of rabbits made severely anemic with phenylhydrazine, *Blood* **14**: 262-273, 1959.
9. Linman, J. W., and Long, M. J.: Erythrocyte osmotic fragility of rats receiving the thermostable plasma erythropoietic factor, *Blood* **13**: 226-238, 1958.
10. Erslev, A. J.: The effect of anemic anoxia on the cellular development of nucleated red cells, *Blood* **14**: 386-398, 1959.
11. Rambach, W. A., Alt, H. L., and Cooper, J. A. D.: The mode of action and nature of a heat stable erythropoietic factor, *Blood* **12**: 1101-1113, 1957.
12. Rambach, W. A., Cooper, J. A. D., and Alt, H. L.: Purification of erythropoietin by ion-exchange chromatography, *Proc. Soc. Exper. Biol. and Med.* **98**: 602-604, 1958.
13. Alpen, E. L., and Cranmore, D.: Cellular kinetics and iron-utilization in bone marrow as observed by Fe-59 radioautography, *Ann. New York Acad. Sc.* **77**: 753-765, 1959.
14. Erslev, A. J.: Erythropoietic function in dilution anemia, *Blood* **10**: 616-622, 1955.

15. Linman, J. W., and Bethell, F. H.: The plasma erythropoietic-stimulating factor in man. Observations on patients with polycythemia vera and secondary polycythemia, *J. Lab. and Clin. Med.* **49**: 113-127, 1957.
16. Contopoulos, A. N., McCombs, R., Lawrence, J. H., and Simpson, M. E.: Erythropoietic activity in the plasma of patients with polycythemia vera and secondary polycythemia, *Blood* **12**: 614-619, 1957.
17. Linman, J. W., and Bethell, F. H.: The plasma erythropoietic stimulating factor. Observations on circulating erythrocytes and bone marrow of rats receiving protein-free extracts of rabbit plasma, *Blood* **11**: 310-323, 1956.
18. Vaquez, M. H.: Sur une forme spéciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante, *Compt. rend. Soc. de biol.* **44**: 384-388, 1892.
19. Saundby, R., and Russell, J. W.: An unexplained condition of chronic cyanosis, with a report of a case, *Lancet* **1**: 515-517, 1902.
20. Osler, W.: Chronic cyanosis, with polycythemia and enlarged spleen: a new clinical entity, *Am. J. M. Sc.* **126**: 187-201, 1903.
21. Lawrence, J. H.: Polycythemia. Physiology, diagnosis and treatment based on 303 cases, *Modern Medical Monographs*, 1955, Grune and Stratton, New York.
22. Calabresi, P., and Meyer, O. O.: Polycythemia vera. I. Clinical and laboratory manifestations, *Ann. Int. Med.* **50**: 1182-1202, 1959.
23. Calabresi, P., and Meyer, O. O.: Polycythemia vera. II. Course and therapy, *Ann. Int. Med.* **50**: 1203-1216, 1959.
24. Berk, L., Burchenal, J. H., Wood, T., and Castle, W. B.: Oxygen saturation of sternal marrow blood with special reference to the pathogenesis of polycythemia vera, *Proc. Soc. Exper. Biol. and Med.* **69**: 316-320, 1948.
25. Schwartz, B. M., and Stats, D.: Oxygen saturation of sternal marrow blood in polycythemia vera, *J. Clin. Investigation* **28**: 736-740, 1949.
26. Lawrence, J. H., Elmlinger, P. J., and Fulton, G.: Oxygen and the control of red cell production in primary and secondary polycythemia: effects on the iron turnover patterns with Fe-59 as tracer, *Cardiologia* **21**: 337-346, 1952.
27. Erslev, A. J., and Laviets, P. H.: Observations on the nature of the erythropoietic serum factor, *Blood* **9**: 1055-1061, 1954.
28. Linman, J. W., and Bethell, F. H.: The effect of irradiation on the plasma erythropoietic stimulating factor, *Blood* **12**: 123-129, 1957.
29. Holmes, H. N., Corbet, R. E., Geiger, W. B., Kornblum, N., and Alexander, W.: The isolation and identification of batyl alcohol and cholesterol from yellow bone marrow, *J. Am. Chem. Soc.* **63**: 2607-2609, 1941.
30. Sandler, O. E.: Some experimental studies on the erythropoietic effect of yellow bone marrow extracts and batyl alcohol, *Acta med. Scandinav. (Suppl. 225)* **133**: 1-72, 1949.
31. Linman, J. W., Bethell, F. H., and Long, M. J.: The erythropoietic stimulatory activity of batyl alcohol, *J. Lab. and Clin. Med.* **52**: 596-604, 1958.
32. Linman, J. W., Long, M. J., Korst, D. R., and Bethell, F. H.: Studies on the stimulation of hemopoiesis by batyl alcohol, *J. Lab. and Clin. Med.* **54**: 335-343, 1959.
33. Berlin, N. I., Lawrence, J. H., and Lee, H. C.: The life span of the red blood cell in chronic leukemia and polycythemia, *Science* **114**: 385-387, 1951.
34. Minot, G. R., and Buckman, T. E.: Erythremia (polycythemia rubra vera). The development of anemia; the relation to leukemia; consideration of the basal metabolism, blood formation and destruction and fragility of the red cells, *Am. J. M. Sc.* **166**: 469-489, 1923.
35. Price-Jones, C.: Red blood cell diameters, 1933, Oxford Medical Publications, London, pp. 74-77.
36. Schulman, I., Pierce, M., Lukens, A., Currimbhoy, Z., and Fort, E.: A factor in normal human plasma required for platelet production: chronic thrombocytopenia due to its deficiency, *Proc. Soc. Ped. Res., Buckhill Falls, Pa.*, May 8-9, 1959, p. 64.

## CLINICAL OBSERVATIONS REGARDING XANTHELASMA \*

By JOSEPH B. VACCA, M.D., WILLIAM A. KNIGHT, JR., M.D., F.A.C.P.,  
and GORONWY O. BROUN, SR., M.D., F.A.C.P., *St. Louis, Missouri*

XANTHELASMA or xanthoma palpebrarum (figure 1) has been reported as being encountered more frequently than is any other type of cutaneous xanthoma.<sup>1</sup> It has been noted to occur in many types of xanthomatosis, especially with xanthoma tuberosum and xanthoma disseminatum,<sup>1</sup> but is believed not to occur with the xanthomatosis associated with essential hyperlipemia.<sup>2</sup> It has been reported to occur in from 10 to 30% of the hypercholesterolemic members of families with familial hypercholesterolemic xanthomatosis,<sup>3, 4, 5, 6, 7, 8, 9</sup> and in up to 80% of the members with xanthomatosis.<sup>2, 9, 10</sup>

While a considerable number of reports are available on familial hypercholesterolemic xanthomatosis,<sup>2-9, 11-17</sup> relatively few are available on persons with xanthelasma as the only type of xanthoma present. Blood cholesterol has been reported to have been significantly elevated in from 40 to 60% of patients with xanthelasma.<sup>1, 10, 18-21</sup> Coronary artery disease has occurred in 34% of cases in one report,<sup>20</sup> and some form of cardiovascular disease was present in 15 to 40% of cases in other reports.<sup>1, 10, 18, 19</sup>

The following study was undertaken to determine more specifically the clinical significance of xanthelasma.

### METHODS AND MATERIALS

Fifty-one consecutive persons with xanthelasma observed in the environs of a general hospital (patients, relatives of patients, visitors, employees, out-patients) by members of the house staff, student body and attending staff were seen by one of us (J. B. V.) during a period of approximately 18 months.

A complete history and a physical examination were obtained on all 51 individuals, with particular emphasis on the following: how long the xanthelasma had been present; size of the xanthelasma; presence of xanthoma elsewhere; evidence of angina pectoris, myocardial infarction, congestive heart failure, heart murmurs, hypertension or diabetes mellitus; menstrual history; evaluation of retinal, cerebral and peripheral vascular status; height and weight; nutritional status; family history of xanthelasma

\* Received for publication March 2, 1959.

From the Department of Internal Medicine, St. Louis University School of Medicine and Firmin Desloge Hospital, St. Louis, Missouri.

Requests for reprints should be addressed to William A. Knight, Jr., M.D., Department of Internal Medicine, Firmin Desloge Hospital, 1325 South Grand Boulevard, St. Louis 4, Missouri.

or xanthoma elsewhere, of coronary artery disease and vascular disease generally.

All individuals had a standard resting electrocardiogram. The majority also had a standard chest roentgenogram. All had at least one determination of the total serum cholesterol.<sup>23</sup> Most had three or more fasting serum cholesterol determinations; an attempt was made to obtain these determinations on consecutive days or clinic visits.



FIG. 1. Xanthelasma (xanthoma palpebrarum). Note lesions at nasal margins of both upper eyelids which have definite yellow coloration.

Nineteen persons had an estimation of the total blood lipids, using the method of Kunkel et al.<sup>24</sup> Thirty-five persons had either a glucose tolerance test or a two-hour postprandial blood sugar, or had previously been discovered to have diabetes mellitus. Moderate elevations of the glucose level in the two-hour blood sample (up to 160 mg.%, Folin-Wu method) were considered to be evidence of "latent" diabetes mellitus.

In only a few instances was it possible to examine any significant num-

ber of relatives of persons found to have xanthelasma. In two cases, relatives found also to have xanthelasma were subsequently included in the study.

### RESULTS

*Age, Sex and Race:* Of a total of 51 persons with xanthelasma, 35 were females and 16 were males. The age distribution by sex is shown in figure 2. There was one Negro female in this series; all others were Caucasian.

*Extrapalpebral Xanthoma:* Only one patient in the series had extrapalpebral xanthoma, a woman who died with myocardial infarction at the age of 47 years, having had angina pectoris since the age of 37 years. She had xanthelasma that almost completely encircled both eyes and a xanthoma on the right Achilles tendon. Her father had had extensive xanthelasma and had died of a myocardial infarction. Her total serum cholesterol was 840 and 870 mg. % on different days.

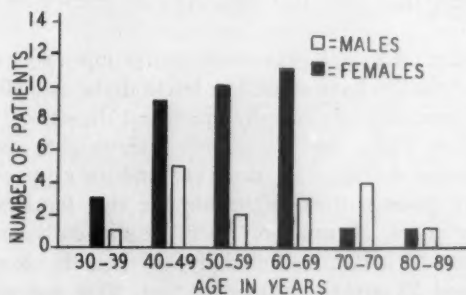


FIG. 2. Distribution by age and sex of 51 individuals with xanthelasma.

*Wasting Diseases:* Eight persons in the series were found to have diseases associated with wasting and malnutrition in addition to having xanthelasma. Of these, three had generalized carcinomatosis; one had severe pulmonary fibrosis and respiratory insufficiency; one had severe thyrotoxicosis (radioactive iodine uptake at 24 hours, 95%); one had far-advanced Laennec's cirrhosis with refractory ascites; one had active lupus erythematosus; one had active, far-advanced pulmonary tuberculosis with severe malnutrition.

*Weight:* The weight of each individual was compared to standard ideal weight tables (Metropolitan Life Insurance Co., Statistical Bureau, June, 1943), and the number of pounds over- or underweight was recorded. Table 1 shows the age and sex distribution of obesity by these criteria. It can be seen that only one male was more than 40 pounds overweight, and that almost 70% of males were less than 20 pounds overweight. Almost 40% of the females were 40 pounds or more overweight, and there were three females who were more than 100 pounds overweight.

TABLE 1  
Age and Sex Distribution of Obesity of 51 Individuals with Xanthelasma

	Males		Females	
	Number	Per Cent	Number	Per Cent
Underweight or normal weight	3	18	7	20
Overweight (lbs.)				
0- 19	8	50	7	20
20- 39	4	25	8	22
40- 59	0	0	7	20
60- 79	0	0	2	6
80- 99	1	6	1	3
100	0	0	3	9
Total	16		35	

*Hypertension:* None of the individuals in this series had significant hypertension (greater than 160/100 mm. Hg) by history or at the time of this study.

*Diabetes Mellitus:* Of the 35 persons of this group who were adequately evaluated, 12 were found to have clinical or latent diabetes mellitus (table 2). One male and five females had clinically important diabetes. The male had had diabetes for four years, was 28 pounds overweight, and required 20 units of NPH insulin daily. The duration and therapy of the diabetes and the number of pounds overweight for the five females with clinical diabetes were: five years, 20 units of NPH insulin daily, normal weight; four years, 20 units of NPH insulin daily, 17 pounds overweight; three years, diet alone, and 12 pounds overweight; less than one year, diet alone, and 22 pounds overweight. Two males and four females were discovered to have "latent" diabetes at the time of this study; all were 20 pounds or more overweight.

All 12 persons found to have diabetes mellitus had had the onset of diabetes after the age of 40 years, were considered to be rather well controlled, and had the "stable" or "adult" type of diabetes mellitus.

*Menstrual History:* Only four of the 35 females included in this series were premenopausal at the time of this investigation; they were 37, 37, 43 and 43 years old. There were nine females in the group who had had their menopause before the age of 45 years; one had had pelvic radiation therapy, a hysterectomy, and bilateral salpingo-oophorectomy for a "tumor" at age

TABLE 2  
Diabetes Mellitus in 35 Individuals with Xanthelasma

	Males	Females
Number tested	11	24
Clinical	1	5
"Latent"	2	4
Diabetes mellitus	3 (27%)	9 (37%)

26 years (age 35 years at the time of this study) without evidence of recurrence of the tumor; five others had had bilateral oophorectomies at ages 42, 38, 35, 32 and 28 years (ages at time of study were 53, 42, 47, 62 and 54 years, respectively); menstruation had ceased spontaneously at ages 40, 40 and 43 years in three other subjects whose ages were 43, 60 and 47 years, respectively.

*Coronary Artery Disease:* The presence of coronary artery disease was ascertained by the following criteria: (1) previous or current myocardial infarction; (2) angina pectoris; (3) congestive heart failure in the absence of other etiologic factors; (4) abnormal electrocardiogram in the absence of other etiologic factors; (5) cardiomegaly by chest roentgenogram in the absence of other etiologic factors.

Table 3 shows the percentages and age at onset of the major clinical manifestation for each sex. Six males and three females had had a myo-

TABLE 3  
Incidence of Coronary Artery Disease by Various Manifestations in  
51 Patients with Xanthelasma

Major Manifestation	Males			Females		
	No.	% of Total	Age at Onset or Discovery	No.	% of Total	Age at Onset or Discovery
Myocardial infarction	6	37.5	39, 36, 55, 44, 60 (angina, 45), 73 (autopsy)	3	8.5	47 (angina, 37), 56, 58 (angina, 50)
Angina pectoris	2	12.5	60, 65	4	11.4	39, 58, 58, 73
Congestive failure	1	6.2	49	0	0	—
Abnormal electrocardiogram	1	6.2	43	8	22.8	43, 43, 47, 60, 60, 60, 61, 65
Cardiomegaly (x-ray)	1	6.2	70	0	0	—
Totals	11	69		15	43	

cardial infarction; two males had had their infarction before the age of 40 years, and one female before the age of 50 years. Six other persons had definite angina pectoris. Eleven persons were considered to have coronary artery disease on the basis of congestive heart failure, abnormal electrocardiogram, or cardiomegaly without any other causative factor implicated. Two patients were not included in this table who were known to have other forms of heart disease (rheumatic valvular heart disease and interatrial septal defect).

The total number of patients with evidence of coronary artery disease by these criteria is 26 (11 males and 15 females). Of the entire group of 51 persons with xanthelasma, 69% of the males and 43% of the females are therefore considered to have coronary artery disease.

*Peripheral Artery Disease:* Six males and four females had evidence of rather severe peripheral arterial disease. One male, 48 years old and a

TABLE 4  
Number of Persons with Xanthelasma by Age and Sex with at Least One Serum Cholesterol Determination Above Levels of 300, 400 and 500 mg. %

Age	Males				Females			
	Total in Group	No. with Cholesterol (mg. %) Above:			Total in Group	No. with Cholesterol (mg. %) Above:		
		300	400	500		300	400	500
30-39	1	0	0	0	3	2	0	0
40-49	5	4	3	0	9	7	4	1
50-59	2	1	0	0	10	9	2	1
60-69	3	2	0	0	11	9	4	1
70-79	4	2	1	1	1	0	0	0
80-89	1	0	0	0	1	1	0	0
Totals	16	9	4	1	35	28	10	3
Per cent	—	56	25	6	—	80	28	9

mild diabetic, had had a mid thigh amputation for gangrene at age 46 years. All of the others in this category had either markedly diminished or absent pulsations of the lower extremities, usually symptomatic.

*Cerebrovascular Disease:* Three males and one female had had cerebrovascular accidents at ages 65, 66, 71 and 55 years, respectively.

*Serum Cholesterol:* Of the entire group of 51 individuals, nine males (56%) and 28 females (80%) had at least one determination of the serum cholesterol that was greater than 300 mg. % (table 4). (Normal values, 150 to 250 mg. %.) Four males (25%) and 10 females (28%) had at least one value greater than 400 mg. %; one male (6%) and three females (9%) had at least one value greater than 500 mg. %.

Using only those individuals who had two or more determinations of serum cholesterol and excluding the individuals with the wasting diseases mentioned above, we found that mean cholesterol values were elevated in percentages quite similar to the values in table 4. The mean cholesterol

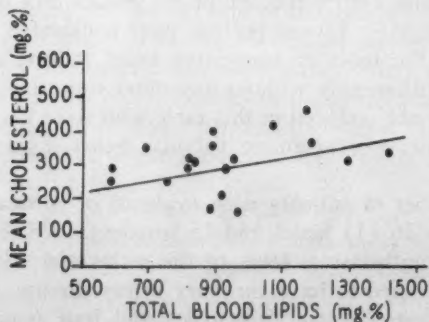


FIG. 3. Relationship of mean serum cholesterol values to total blood lipids for 19 individuals with xanthelasma.

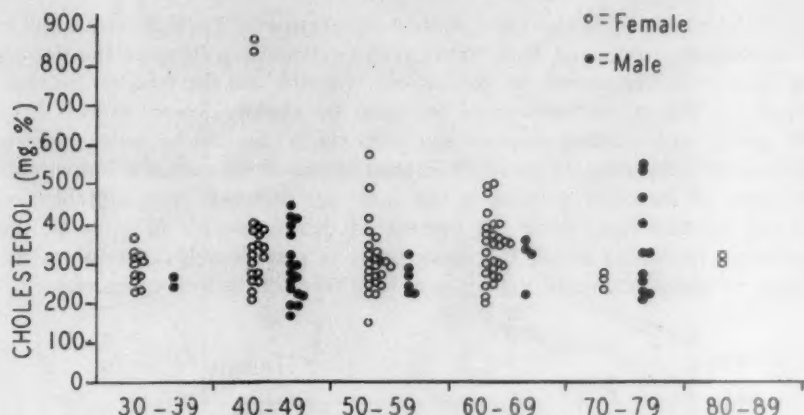


FIG. 4. Individual serum cholesterol values by sex and age for 51 individuals with xanthelasma.

was above 300 mg.% in six of 10 males (60%) and above 400 mg.% in two (20%); 23 of 29 females had mean cholesterol values above 300 mg.% (80%); they were above 400 mg.% in four (13%) and above 500 mg.% in two (6%).

**Total Blood Lipids:** Of the 19 persons on whom total blood lipid values are available, 15 had abnormally high values. However, while the majority had elevated total blood lipids, 10 of the elevated values were below 1,000 mg.% (normal range, 530 to 760 mg.%). The greatest elevation was 1,412 mg.%.

Figure 3 suggests that there is a general relationship between mean total serum cholesterol and total blood lipids, i.e., a general trend exists for higher mean cholesterol values in association with higher total lipid values.

**Relationship of Age to Total Serum Cholesterol:** Figure 4 shows individual cholesterol determinations plotted against age for the 51 persons with xanthelasma. There seems to be a tendency toward increase of cholesterol levels in both sexes with increasing age, although this is not very striking. In some of the age groups there are only a few determinations.

TABLE 5  
Comparison of Mean Cholesterol Determinations in Cachectic and Noncachectic Individuals With Xanthelasma, by Age and Sex

Age and Sex	Cachectic		Not Cachectic	
	No. of Det'ns	Mean Cholesterol (mg.%)	No. of Det'ns	Mean Cholesterol (mg.%)
40-49, males	2	219	16	309
40-49, females	13	267	22	368
50-59, females	4	304	27	320
70-79, males	6	255	11	346

*Relationship of Weight and Nutritional Status to Total Serum Cholesterol:* Figure 5 does not seem to suggest a relationship between the degree of obesity (as the number of pounds overweight) and the total serum cholesterol. The serum cholesterol tends to be slightly lower, however, in the group with wasting diseases and cachexia. This can be better demonstrated by comparing the mean cholesterol values of the cachectic individuals to those of the other persons in the same age and sex groups (table 5). It can be seen that, while the number of determinations in some of the cachectic groups is small, the mean value is considerably lower than the mean for the noncachectic groups in at least three of the four categories.

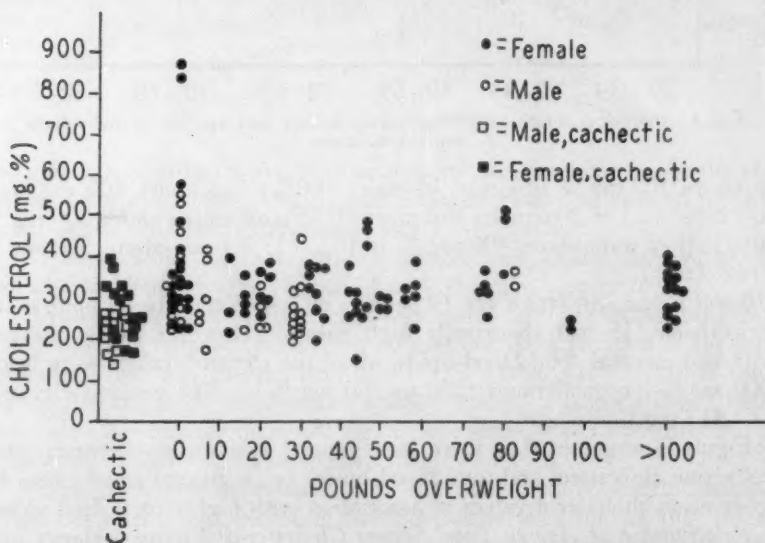


FIG. 5. Comparison of serum cholesterol values according to degree of obesity (pounds overweight) and nutritional status in 51 persons with xanthelasma.

*Relationship of Size of Xanthelasma to Total Cholesterol Values:* Figure 6 represents the association of individual cholesterol values to the estimated size of the xanthelasma in square millimeters. For both sexes there seems to be a relationship, i.e., higher cholesterol values generally are associated with the larger xanthelasma.

*Relationship of Mean Cholesterol Values to Variation of Serum Cholesterol Values:* It was noted early in the course of this study that there was considerable variation of the cholesterol values from day to day and from week to week in many persons with xanthelasma. Figure 7 demonstrates the relationship between the mean cholesterol value and the maximal observed variation in cholesterol determinations for individuals in whom at least three determinations were obtained. There seems to be a relationship

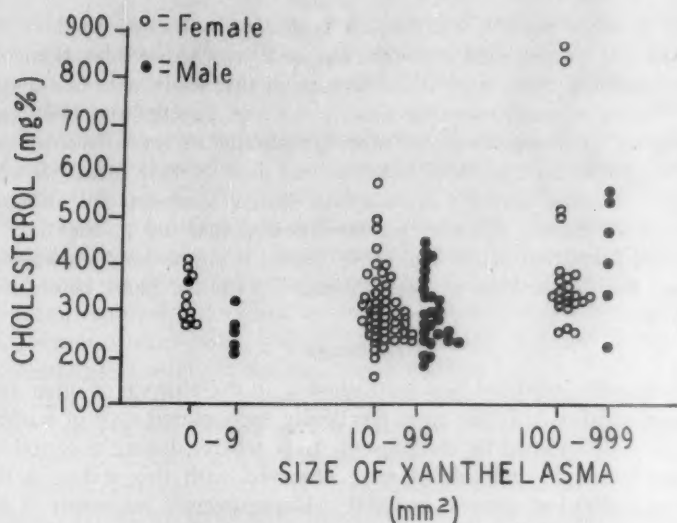


FIG. 6. Relationship between individual serum cholesterol values and size of xanthelasma (square millimeters).

such that, as the mean cholesterol value increases, the variation of serial determinations increases.

*Family History of Xanthoma and of Prominent Vascular Diseases:* It was not possible personally to conduct complete family surveys for xanthoma and hypercholesterolemia. However, in most cases the interest and cooperation of individuals included in this study enabled us to obtain fairly complete information on the presence or absence of xanthelasma and cardiovascular disease in the families. There were five cases in whom there was a definite family history of xanthelasma in association with cardiovascular

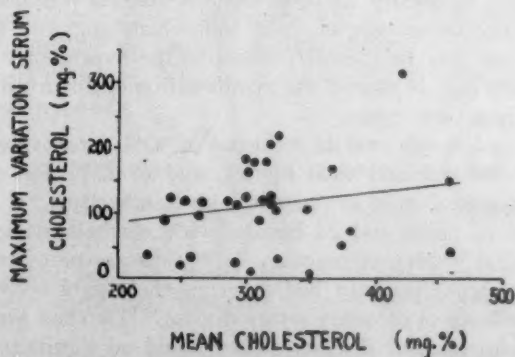


FIG. 7. Relationship between mean cholesterol values and the maximal observed variation in cholesterol determinations in 33 persons with xanthelasma.

disease; in addition, one individual's brother was known to have tendon xanthoma and to have died in middle age of a myocardial infarction.

Besides these, there were three persons in this study who had a striking family history of cardiovascular disease without any definite knowledge of the presence of xanthelasma or other xanthoma in the affected relatives. One woman's father and three brothers had died in their fifties with "heart attacks." Another person's brother had died of a myocardial infarction at the age of 40 years. Another person reported that her mother had had a myocardial infarction at the age of 49 years; her grandmother was said to have had the "same kind of heart trouble," with the onset before the age of 40 years.

#### DISCUSSION

Montgomery reported that xanthelasma, in the absence of other types of cutaneous xanthoma, is the most frequently encountered type of xanthoma.<sup>1</sup> This was substantiated by the present study where, during a period of less than two years, 51 individuals were observed with this lesion in the environs of a 300-bed general hospital. Montgomery's statement is further strengthened by the fact that in only two instances were two members of the same family used in this study. During this same period of time only two cases were observed with extrapalpebral xanthoma, even though they were being searched for; one of these had a tendon xanthoma in addition to xanthelasma and is included in this study; the other patient had tendon xanthoma without xanthelasma.

A review of the literature suggests that persons with xanthelasma are considered to have this finding as a manifestation of familial hypercholesterolemic xanthomatosis exclusively. While this cannot be disproved in the subjects of the present series, because of insufficient family studies, we are certainly impressed by the lack of a family history of xanthoma and of prominent cardiovascular disease in the majority of cases. On the other hand, the finding of obesity, diabetes mellitus and the postmenopausal state in a rather large percentage of these individuals suggests the possibility that these factors may be causally related to the hypercholesterolemia, and that xanthelasma may be merely the manifestation of disturbed lipid metabolism of possibly several types.

Montgomery has reported an incidence of 40% for elevated blood lipids (both total cholesterol and total lipids), and of 25% for elevated lipids with cardiovascular disease in persons with xanthelasma.<sup>1, 10, 18, 19</sup> Epstein et al.<sup>20</sup> studied 12 males and 23 females with xanthelasma and noted that 15 had a familial history of coronary artery disease or of cerebrovascular disease. Forty-seven per cent had a serum cholesterol above 300 mg.%. Twelve had evidence of coronary artery disease. Two had peripheral artery disease or cerebrovascular disease. They found no significant abnormality in the lipoprotein patterns in the patients with xanthelasma. Curtis and Berger<sup>21</sup> found the total serum cholesterol to be above normal (90 to

171 mg.%) in 58% of 26 persons with xanthelasma, and the total lipids to be above normal (360 to 600 mg.%) in 66% of 39 persons with xanthelasma. They found similar percentages of abnormalities for free cholesterol and phospholipids.

Our data on the sex ratio and occurrence of obesity are in close agreement with the above studies. The over-all incidence of elevated cholesterol values in our series (73% greater than 300 mg.%) is somewhat higher than that reported by the above authors. The 79% incidence of increased total blood lipids (only one determination done for each individual) is comparable to the 66% incidence reported by Curtis and Berger.<sup>21</sup> While xanthelasma reportedly does not occur with xanthomatosis associated with a milky serum, it does occur with a hyperlipemia of a milder degree which is apparently not entirely in the cholesterol fraction.

The fluctuation of the serum cholesterol values in these persons is impressive. Steiner and Domanski<sup>22</sup> reported in 1943 that serum cholesterol values were inconstant and fluctuated widely in persons with coronary artery disease, whereas normal persons demonstrated a relative constancy of values. While we could find no reports on this specifically in persons with xanthelasma, the data presented in several studies of patients with hypercholesterolemic xanthomatosis with lesions other than xanthelasma show striking variations of cholesterol levels in at least some individuals.<sup>2,17</sup>

The incidence of coronary artery disease in our series is considerably higher than that reported either by Montgomery<sup>1, 10, 18, 19</sup> or by Epstein and his associates.<sup>20</sup> Using criteria similar to those we have employed, Epstein found approximately 35% to have coronary artery disease, as compared to approximately 50% in our series.

As has been previously emphasized, the finding of xanthelasma on physical examination should alert one to the probability of the patient's having hypercholesterolemia and hyperlipemia, and occlusive vascular disease of the coronary circulation in particular. The size of the cutaneous lesions seems to be, in general, a guide to the severity of the basic lipid abnormality and the probability of premature vascular disease. The finding of xanthelasma should likewise alert one to the possibility of a familial problem of hypercholesterolemia.

#### SUMMARY AND CONCLUSIONS

1. Fifty-one persons (35 females and 16 males) with xanthelasma have been studied.
2. Thirty-eight per cent of the females in this series were more than 40 pounds overweight, whereas only 6% of the males were this much overweight.
3. Thirty-four per cent of those tested had clinical or latent diabetes of the adult type.

4. Thirty-one of the 35 females with xanthelasma were postmenopausal at the time of this study; nine females had had their menopause before the age of 45 years.

5. Seventy-three per cent of the group had a serum cholesterol level greater than 300 mg.%; 79% of those who were tested had mild to moderate elevations of total blood lipids.

6. Evidence of coronary artery disease was present in 69% of the males and 43% of the females; peripheral vascular disease occurred in 20% and cerebrovascular disease in 8% of the series.

7. The occurrence of cachexia or a wasting disease in a person with xanthelasma was associated with a lesser elevation of blood lipids.

8. A general relationship between the size of the xanthelasma and the cholesterol level was suggested.

9. A striking variation of serum cholesterol levels was observed in many of the individuals studied. The degree of fluctuation seemed to be related to the mean cholesterol level.

10. A family history of xanthoma (including xanthelasma) or of prominent vascular disease was obtained in a minority of individuals.

#### ACKNOWLEDGMENTS

We wish to thank the members of the house staff and attending staff of Firmin Desloge Hospital and the Junior and Senior medical students of St. Louis University School of Medicine, all of whom directed our attention to most of these cases. We particularly wish to thank Dr. Henry Oppenheimer and his associates in the Diabetes Clinic. We also thank Sister Mary Laureen Harris, S.S.M., for valuable technical assistance.

#### SUMMARY IN INTERLINGUA

Varie aspectos clinic esseva investigate in 51 subjectos con xanthelasma (16 masculos, 35 femininas). Octo del subjectos habeva in plus morbos debilitatori. Solamente un habeva xanthoma extrapalpebral.

In le majoritate del casos, al minus tres determinationes del cholesterol total del sero esseva effectuate in tres consecutive dies o visitas. In 56% del masculos e in 80% del femininas al minus un del determinationes monstrava un valor de plus que 300 mg pro 100 ml. In 25% del masculos e 28% del femininas, al minus un valor esseva plus que 400 mg per 100 ml e in 6% del masculos e 9% del femininas plus que 500 mg per 100 ml.

Il pareva existir pauc o nulle correlation inter le etate del patientes e le nivello de cholesterol. Sed il existeva un correlation inter le nivellos de cholesterol e le dimensiones del xanthelasma. Frappante variationes del nivellos de cholesterol in subjectos individual esseva notate. Iste variationes esseva le plus grande in subjectos con alte valores medie del concentration de cholesterol in le sero. Evidentia de morbo del arteria coronari esseva trovate in 69% del masculos e in 43% del femininas. Morbo de arteria peripheric e cerebral esseva trovate in 10 homines e 4 feminas. Un historia familial de xanthoma cutanee o de prominente morbo vascular esseva obtenite in solmente sex homines e octo feminas.

Inter le 35 patientes testate pro diabete mellite le incidentia de resultados positive esseva 27% pro masculos e 37% pro femininas. Trenta-un del feminas habeva passate le menopause. Iste total include 10 in qui ille evento habeva essite prematur.

Es concludite que xanthelasma non es incommun, que illo occurre primarimente in obese feminas postmenopausal, e que illo es usualmente associate con elevate ni-

vellos de cholesterol seral e morbo de arteria coronari. Durante que xanthelasma pote occurrer como manifestation de familial xanthomatosis hypercholesterolemic, numeros significative de pacientes con xanthelasma ha altere disordines le quales es frequentemente associate con augmentos de atherogenese (obesitate, diabete, menopause precoce, etc.).

## BIBLIOGRAPHY

1. Montgomery, H.: Cutaneous manifestations of diseases of lipid metabolism, *M. Clin. North America* **24**: 1249, 1940.
2. Lever, W., Smith, P., and Hurley, N.: Idiopathic hyperlipemic and primary hypercholesterolemic xanthomatosis, *J. Invest. Dermat.* **22**: 33, 1954.
3. Adlersberg, D.: Hypercholesterolemia with predisposition to atherosclerosis, *Am. J. Med.* **11**: 600, 1951.
4. Fliegelman, M., Wilkinson, C., Jr., and Hand, E.: Genetics of xanthoma tuberosum multiplex, *Arch. Dermat. and Syph.* **58**: 409, 1948.
5. Wilkinson, C.: Essential familial hypercholesterolemia; cutaneous, metabolic, and hereditary aspects, *Bull. New York Acad. Med.* **26**: 670, 1950.
6. Wheeler, E., and Sprague, H.: The prevalence and significance of hypercholesterolemia among children and siblings of patients with hypercholesterolemic xanthomatosis, *J. Clin. Investigation* **32**: 611, 1953.
7. Wheeler, E.: The genetic aspects of atherosclerosis, *Am. J. Med.* **23**: 653, 1957.
8. Leonard, J.: Hereditary hypercholesterolemic xanthomatosis, *Lancet* **2**: 1239, 1956.
9. Piper, J., and Orrild, L.: Essential familial hypercholesterolemia and xanthomatosis, *Am. J. Med.* **21**: 34, 1956.
10. Montgomery, H., and Osterberg, A.: Xanthomatosis. Correlation of clinical, histopathologic, and chemical studies of cutaneous xanthoma, *Arch. Dermat. and Syph.* **37**: 373, 1938.
11. Rigdon, R., and Willeford, G.: Sudden death during childhood with xanthoma tuberosum, *J. A. M. A.* **142**: 1268, 1950.
12. Svendsen, M.: Are supernormal cholesterol values in serum caused by a dominantly inherited factor? *Acta med. Scandinav.* **104**: 235, 1940.
13. Boas, E., Parets, A., and Adlersberg, D.: Hereditary disturbance of cholesterol metabolism: a factor in the genesis of atherosclerosis, *Am. Heart J.* **35**: 611, 1948.
14. Boas, E., and Adlersberg, D.: Familial hypercholesterolemia (xanthomatosis) and atherosclerosis, *J. Mt. Sinai Hosp.* **12**: 84, 1945.
15. Adlersberg, D., and Parets, A.: Genetics of atherosclerosis, *J. A. M. A.* **141**: 246, 1949.
16. Muller, C.: Angina pectoris in hereditary xanthomatosis, *Arch. Int. Med.* **64**: 675, 1939.
17. Alvard, R.: Coronary heart disease and xanthoma tuberosum associated with hereditary hyperlipemia, *Arch. Int. Med.* **84**: 1002, 1949.
18. Montgomery, H. V.: Cutaneous xanthomatosis, *Ann. Int. Med.* **13**: 671, 1939-40.
19. Montgomery, H., in Discussion, Epstein, N. N., Rosenman, R. H., and Gofman, J. W.: Serum lipoproteins and cholesterol metabolism in xanthelasma, *Arch. Dermat. and Syph.* **65**: 70-81, 1952.
20. Epstein, N., Rosenman, R., and Gofman, J.: Serum lipoproteins and cholesterol metabolism in xanthelasma, *Arch. Dermat. and Syph.* **65**: 70, 1952.
21. Curtis, A., and Berger, J.: Effect of feeding a lipotropic substance to patients with xanthelasma, *Arch. Dermat. and Syph.* **52**: 252, 1945.
22. Steiner, A., and Domanski, B.: Serum cholesterol level in coronary arteriosclerosis, *Arch. Int. Med.* **71**: 397, 1943.
23. Brown, H., Zlatkis, A., Zak, B., and Boyle, A.: Rapid procedure for determination of free serum cholesterol, *Anal. Chem.* **26**: 397, 1954.
24. Kunkel, H., Ahrens, E., and Eisenmenger, W.: Application of turbidometric methods for estimation of gamma globulin and total lipids to the study of patients with liver disease, *Gastroenterology* **11**: 499, 1948.

## DRUGS IN EMOTIONAL DISORDERS: PAST AND PRESENT \*

By LEO E. HOLLISTER, M.D., F.A.C.P., *Palo Alto, California*

WIDESPREAD interest in drugs currently used for treating emotional disorders has created the erroneous impression that pharmacologic approaches to psychiatric treatment are something new. Both the number and the variety of drugs employed in the past have been large. The present review will cover only those agents used for functional emotional disorders within the last 20 years, first considering briefly the older treatments. The fact that each of these has been described as ameliorating the course of emotional illness emphasizes the difficulty of evaluating such treatment. This aspect of drug therapy is still unchanged.

The second purpose of this review will be to consider drugs presently used for treating emotional disorders. Some of these drugs are in fact new, both in their chemical structures and in their pharmacologic actions. Others are closely related to previous agents, as will be evident. The popularity of the new drugs has not diminished with time, their therapeutic effects being quite genuine in a wide variety of emotional illnesses. Considerable argument still exists concerning their role in the total treatment of these disorders.

Finally, we shall consider the enlarging series of psychotomimetic agents. These drugs, though not often applied therapeutically, are believed to be useful tools for investigating psychologic, neurophysiologic and biochemical phenomena of disturbed mental function.

### DRUGS IN EMOTIONAL DISORDERS: PAST

The aims of drug therapy in emotional disorders a decade ago were analogous to those of the present. They may be categorized as follows:

1. Calming anxious or disturbed patients, an effect formerly called sedation, currently named tranquilization. A logical extension of this procedure was inducing sleep, the so-called "sleep therapies."
2. Production by drugs of either convulsive or nonconvulsive shock therapy, rather than convulsive therapy initiated by electroshock.
3. Amelioration of depressed states by stimulation of the central nervous system.
4. Facilitation of psychotherapy by decreasing inhibitions and affording emotional release.

\* Received for publication June 1, 1959.

From the Medical Service, Veterans Administration Hospital, Palo Alto, California.

Requests for reprints should be addressed to Leo E. Hollister, M.D., Chief, Medical Service, Veterans Administration Hospital, Palo Alto, California.

5. Drugs, hormones, vitamins and other natural products given for postulated specific deficiencies, or based on certain hypotheses regarding mental abnormalities.

Table 1 lists drugs formerly used for tranquilization or sleep therapy, and for convulsive or nonconvulsive shock therapy. Most common central nervous system depressants have been used for tranquilization, including anticonvulsant, antihistaminic and muscle-relaxant agents.<sup>1-3</sup> As most of the latter drug groups produce sedation as a "side-effect," this application is entirely rational. The production of convulsions with insulin or convulsant drugs such as pentylenetetrazol was a common procedure for many years. Phenomena similar to convulsions have been induced by carbon dioxide, histamine, atropine, cholinergic drugs, or anticholinesterases.<sup>4-6</sup>

TABLE 1  
Drugs in Emotional Disorders: Past

*Tranquilization or sleep therapy*

Barbiturates—all kinds, all modes of administration  
Chloral hydrate  
Alcohol or ether—IV  
Nitrous oxide  
Trimethadione, diphenylhydantoin  
Mephesisin  
Promethazine, tripeleminamine, diphenhydramine, methapyrilene  
Methylparafynol

*Convulsive or non-convulsive shock*

Insulin  
Pentylenetetrazol (metrazol)  
Carbon dioxide  
Histamine  
Atropine  
Acetylcholine, diisopropylfluorophosphate, sodium glutamate  
Dinitrile succinate, malononitrile,

Table 2 lists drugs formerly (some still) used for treating mental depression or for facilitating psychotherapy. Most known central nervous system stimulants have been tried in treating mental depression, sometimes in combination or in sequence with a sedative.<sup>7,8</sup> Aside from direct stimulation, euphoriant effects from cannabis analogues,<sup>9</sup> or shock effects from the fever-producing agent, pyromen, have also been tried. Drugs facilitating psychotherapy have been either central nervous system stimulants or depressants. Thus, such contrasting drug groups as the amphetamines and the barbiturates have both been used for this purpose, separately or together.<sup>10,11</sup> Psychotomimetic drugs such as lysergic acid diethylamide,<sup>12</sup> trimethoxyphenyl ethylamine (mescaline) and scopolamine have been reputed to release inhibitions, enabling the patient to relate conflictual material freely. If abreaction occurred, the beneficial effects were said to be increased.

Table 3 lists various other treatments. Those agents listed above the dotted line have been tried in this country, those below the dotted line only

TABLE 2  
Drugs in Emotional Disorders: Past

*Anti-depressives*

Caffeine	} alone or combined with barbiturates
Desoxyephedrine	
Amphetamines	
Ether—IV	
Nicotinic acid	
Isoniazid, iproniazid	
Lactic acid	
Cannabis analogues	
Pyromen	
Prostigmine	

*Facilitation of psychotherapy*

Lysergic acid diethylamide  
 Trimethoxyphenylethylamine, trimethoxyamphetamine  
 Scopolamine  
 Amphetamines, desoxyephedrine  
 Chloroform, trichloroethylene, somnoform  
 Alcohol or ether—IV  
 Nitrous oxide  
 Sodium amytal or pentothal  
 Mephenesin

abroad. Some investigators have tried to relate epinephrine to anxiety, attempting to develop tolerance by desensitization, or to block its effects by agents such as Dibenzylamine or ergotamine.<sup>13, 14</sup> The rationale for vitamins was based on the appearance of vague symptoms, somewhat analogous to those of psychoneuroses, in experimentally produced vitamin deficiency. Virtually every vitamin known has been tried at one time or another. In the case of hormones, the usual postulate was that one or more is deficient, usually sex hormones, adrenal hormones or thyroid hormones. Replacement therapy was supposed to assist the patient to function better in all

TABLE 3  
Drugs in Emotional Disorders: Past

*Miscellaneous*

Adrenaline desensitization or tolerance  
 Dibenzylamine, ergotamine  
 Nikethamide  
 Vitamins—most, including vitamins E and B<sub>12</sub>  
 Hormones: sex hormones  
     adrenal steroids  
     thyroid, thyroxine  
     pitressin  
 Procaine—IV, intracerebral or intraventricular  
 .....  
 Lithium salts, strontium bromide  
 Ammonium sulfate, magnesium sulfate  
 Aminopyrine—IV  
 Honey or dextrose—IV  
 Serotonin  
 Tuberculin cutaneous allergic shock  
 Antireticular cytotoxic serum  
 Incompatible blood transfusion  
 Epiphysial or placental extracts

spheres, including the mental. Perusal of some of these treatments suggests the degree of desperation to which physicians may be driven in attempting to treat emotional disorders. Some treatments proved to be highly dangerous, such as the administration of lithium salts or incompatible blood transfusions. Others bordered on the ridiculous, such as the intravenous infusion of honey or the parenteral administration of epiphysial or placental extracts.

#### DRUGS IN EMOTIONAL DISORDERS: PRESENT

Currently, three classes of drugs are being used either in treating emotional disorders or in studying phenomena associated with them. These groups are: (1) tranquilizing drugs; (2) agents for treating depressed patients, sometimes alluded to as stimulants, antidepressants or "psychic energizers"; and (3) psychotomimetic drugs, which induce some of the symptoms of emotional disorders.

#### TRANQUILIZING DRUGS

Most drugs accepted as being tranquilizers fall into four categories, based on chemical structure: (1) phenothiazine derivatives; (2) Rauwolfia alkaloids; (3) diphenylmethane derivatives, and (4) glycerol derivatives. As the term "tranquilizer" becomes broader in its implications, additional types of chemical structure may be represented. Actually, obtaining an adequate definition of these drugs is still a major difficulty. Some investigators see little difference between tranquilizers and conventional sedatives; others stress that tranquilizers act primarily subcortically and do not enforce sleep, in contrast to the older sedatives. Additional descriptions of the properties of a tranquilizing drug have been selected, often arbitrarily, on the basis of known pharmacologic actions of specific tranquilizers. Such criteria include inability to produce anesthesia, a tendency to increase muscle tone, lowering of convulsive threshold, absence of excitement, and a negligible addiction liability.

Phenothiazine derivatives, which were among the earliest categorized as tranquilizers, are the most important group. Their effectiveness in severe emotional disorders has led to a rapid growth in their numbers. The chemical structures of several tranquilizing phenothiazines currently available are shown in figure 1. All share the phenothiazine nucleus, which can be substituted at two places, the carbon atom at the 2-position or the nitrogen atom at the 10-position. A halogen, either a chlorine atom or a trifluoromethyl group, is frequently substituted at the 2-position. Other substitutions made at this position have been methoxy, acetyl, thiomethyl, dimethylsulfonamide and other organic radicals. The "tail" of the compound, placed at the 10-position, may be either aliphatic (straight-chain) or aromatic (containing a ring structure). Chlorpromazine, promazine and trifluprom-

azine have the same aliphatic (dimethylaminopropyl) "tails." Aromatic "tails" include the piperidine ring (as in mepazine and thioridazine), or the piperazine ring (as in prochlorperazine, trifluoperazine, perphenazine, fluphenazine and thiopropazate). It is significant that in each of the tranquilizing phenothiazines the nitrogen atom of the "tail" is separated from the nitrogen atom in the phenothiazine ring by three carbon atoms.

### PHENOTHIAZINE DERIVATIVES

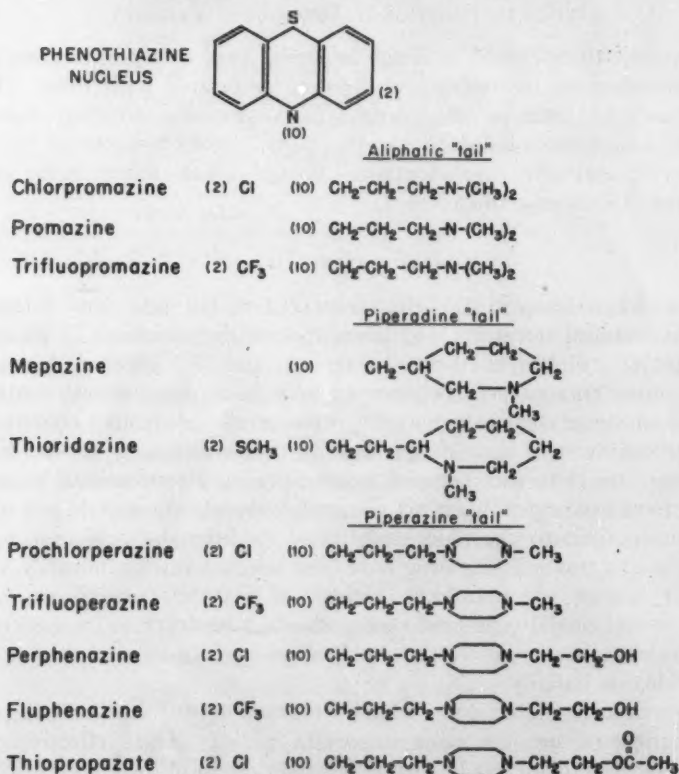


FIG. 1.

Related phenothiazine derivatives have been grouped together in figure 1. Promazine, chlorpromazine and trifluopromazine differ only in the type of substitution at the 2-position of the phenothiazine nucleus. Thioridazine differs considerably from the other piperidine derivative, mepazine, first, in having a thiomethyl group substituted on the nucleus, and second, in having a longer connecting group in the "tail." The piperazine derivatives are multiplying most rapidly now. Prochlorperazine and trifluoperazine are

alike except for the different halogen substitutions. The same relationship obtains between perphenazine and fluphenazine. Thiopropazate is similar to perphenazine except for an additional acetyl group in the "tail" structure.

The importance of these chemical substitutions on the pharmacologic action of the phenothiazine derivatives is still not fully assessed. In general, substitution at the 2-position enhances lipid solubility of the compound, indirectly enhancing potency in terms of dose. Thus, unsubstituted compounds such as promazine and mepazine are weaker than their substituted analogues. Trifluoromethyl substitution enhances potency more than a single chlorine atom does. The piperazine derivatives are more potent than

#### RAUWOLFIA ALKALOIDS

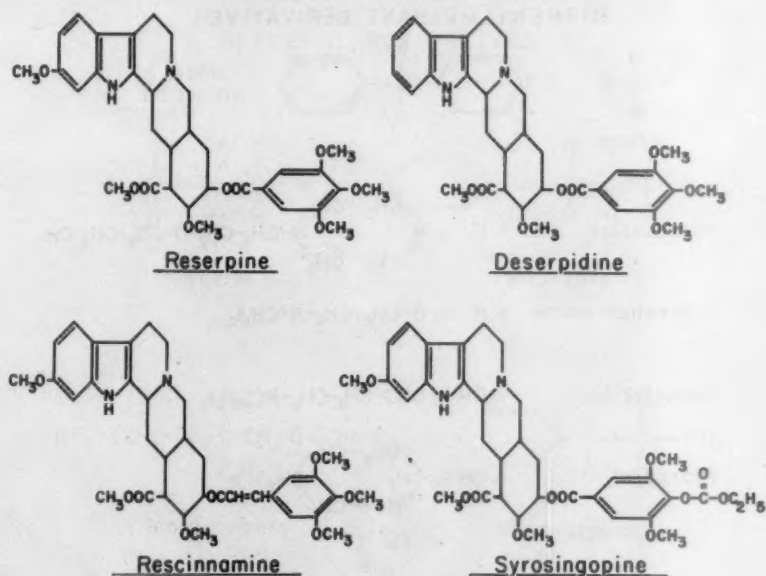


FIG. 2.

compounds with aliphatic or piperidine "tails." The piperazine drugs also tend to produce more extrapyramidal effects than do the other two groups.

Despite the increased potency of the newer phenothiazine tranquilizers, it is probable that little therapeutic advantage has been gained. It is a common fallacy to assume that increased potency means increased therapeutic effect. In general, the trend to more potent tranquilizers (as well as corticosteroids) has raised as many problems as it has solved. Controlling dosage usually becomes a greater problem as potency is increased. Side-effects lost are often replaced by new ones or the increase of old ones. The only apparent exception among the newer phenothiazine tranquilizers is

thioridazine, which singularly lacks extrapyramidal effects, yet is therapeutically efficacious.

Rauwolfia alkaloids, also among the first to be recognized as tranquilizing drugs, have become less important in treating emotional illness. Most of the therapeutic effects of these alkaloids can be obtained more quickly and frequently from the phenothiazine derivatives. In many respects it is unfortunate that the Rauwolfia alkaloids did not have longer clinical use or laboratory investigation. These alkaloids still play a role in the treatment of hypertension. Among nearly three dozen alkaloids found in the plant *Rauwolfia serpentina*, the four shown in figure 2 are currently in use. As can be seen from the structural formulas, these alkaloids have complex

#### DIPHENYLMETHANE DERIVATIVES

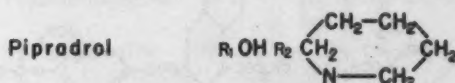
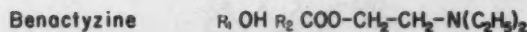
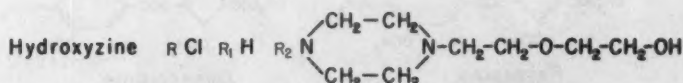
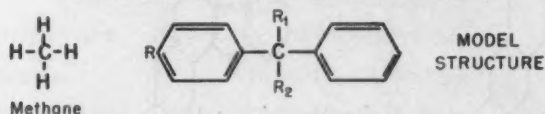


FIG. 3.

structures, differentiated by minor modifications. The newest of these alkaloids, syrosingopine, has been produced synthetically. This particular alkaloid is alleged to have specific hypotensive effects without the tranquilizing effects of the others. If this dissociation of pharmacologic effects has really been achieved, it required a minimum of chemical change. The pharmacologic actions of whole root extracts or the alseroxylon fraction of *Rauwolfia* (containing all the alkaloids) is so similar to those of the individual alkaloids as to suggest that the latter provide the major portion of the activity.

The diphenylmethane derivatives are a group of drugs with diverse pharmacologic actions. Some with sedative properties are considered to be tranquilizing drugs. In figure 3 the model structure of this series of

drugs is shown, as well as the substitutions which produce four of them. Hydroxyzine is a sedative drug which also has antihistaminic properties. Other drugs of this series, such as diphenhydramine, are known primarily as antihistaminics, with the "side-effect" of sedation. As mentioned earlier, antihistaminic drugs were used for tranquilization in the past. Benactyzine has been used for treating various psychoneuroses, although its pharmacologic actions and side-effects are primarily those of an anticholinergic. It differs from adiphenine, one of the earliest synthetic anticholinergics, only in lacking an oxygen atom. To demonstrate still further the diversity of the diphenylmethanes, pipradol, a derivative with a piperidine ring, is a mild stimulant. Its gamma isomer, azacyclonol, has been said to be a tranquilizing drug, reputedly calming patients and relieving hallucinations.

### GLYCEROL DERIVATIVES

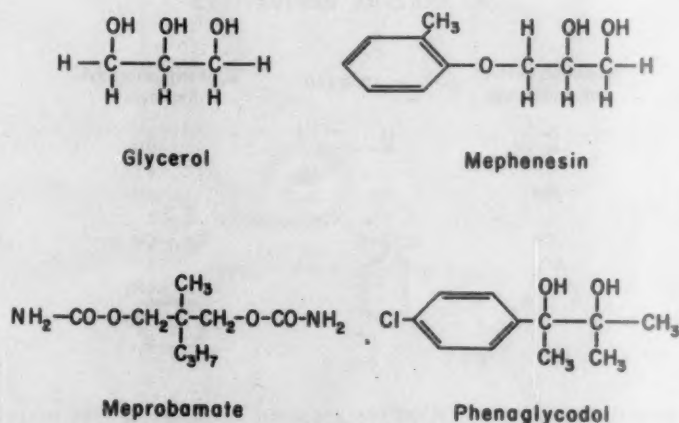


FIG. 4.

However, many clinical investigators have been hard put to find any definite pharmacologic or therapeutic action for this agent.

Some glycerol derivatives are now considered to be tranquilizers, although originally a series of muscle-relaxant drugs. In figure 4 the relationships between three of these drugs and glycerol are shown. Mephenesin, one of the earliest of the glycerol derivatives, was primarily used as a muscle relaxant, though also used for emotional illnesses. Its mild effect at the usually recommended dosage and its brief duration of action made it disappointing clinically. Meprobamate resulted from an effort to improve upon the muscle-relaxant actions of mephenesin. Whether such improvement has been obtained is still a matter of discussion, but in any case the

sedative effects of meprobamate are greater. The fact that some of its central action is subcortical, and that sedation from it does not seriously impair mental functions, has led to its consideration as a tranquilizer. Phenaglycodol is a similar derivative, with actions akin to those of meprobamate.

A voluminous literature has already been compiled in regard to the clinical effects, pharmacologic actions and complications of the tranquilizing drugs. Few drugs have been as extensively studied so soon after their introduction as chlorpromazine. We shall not attempt here to review this material, which has been done very well elsewhere.<sup>15-21</sup>

#### ANTIDEPRESSANT AGENTS

Besides the conventional central nervous system stimulants, two new classes of drugs have been developed recently for treating the symptom of mental depression. The first group is the hydrazide derivatives, whose

#### HYDRAZIDE DERIVATIVES

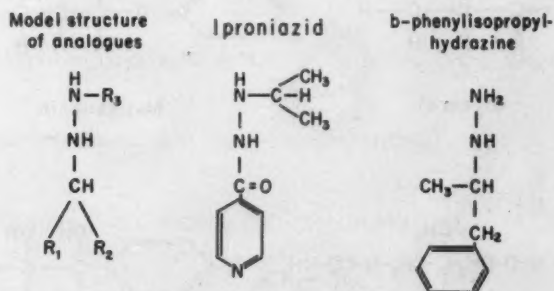


FIG. 5.

model structure and two derivatives are seen in figure 5. It may be recalled that iproniazid was first used as an antibacterial in treating tuberculosis. One of the side-effects was the production of a euphoric or stimulated state. Because of this and other toxic effects, the drug was soon replaced by isoniazid. Both iproniazid and isoniazid were subsequently tried in mental patients, but the results were generally not encouraging.<sup>22</sup> Recently, iproniazid has been revived as an antidepressant agent. The increasing number of encouraging clinical studies has led to the development of a great many analogues. One of the new analogues, b-phenylisopropylhydrazine, is shown in the figure. This drug is of especial interest because it is the hydrazine analogue of the older stimulant, amphetamine. Besides application in treating mental depression, the hydrazide derivatives have also been studied in the treatment of angina pectoris, hypertension, rheumatoid arthritis, psoriasis and other clinical entities.<sup>23, 24</sup>

The second new group of antidepressant agents, the iminodibenzyl derivatives, is closely related to the phenothiazine drugs. Originally this class of drugs was developed to treat the same spectrum of mental or emotional disorders as the phenothiazine derivatives. In figure 6 the relationship between the phenothiazine nucleus and the iminodibenzyl nucleus is shown. Sharing as they do the same "tail" structure, promazine and imipramine are similar chemically. Imipramine was disappointing as a treatment for schizophrenia, but appeared to benefit patients who were depressed.<sup>25, 26</sup> If its worth as an antidepressant is corroborated by further clinical trials, one can almost certainly predict what will happen: the iminodibenzyl derivatives will multiply as rapidly as the phenothiazines.

A rather simple chemical structure, dimethylaminoethanol (deanol), is reputed to be a stimulant in normal persons, and to ameliorate the symptoms

#### RELATIONSHIP BETWEEN PHENOTHIAZINE DERIVATIVES AND IMINODIBENZYL DERIVATIVES

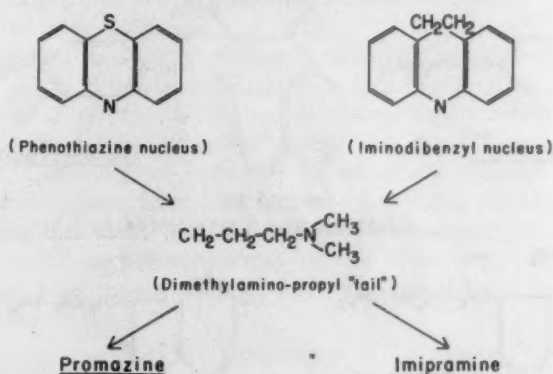


FIG. 6.

of mental depression in patients.<sup>27</sup> This drug readily passes the blood-brain barrier, acting as a precursor for formation of increased acetylcholine in the brain. Clinical studies have been so few that it is difficult as yet to assign it a proper place as an antidepressant.

#### PSYCHOTOMIMETIC DRUGS

When discussing psychotomimetic drugs, one again has problems regarding definitions. There are many drugs which affect mental states in one way or another. Generally speaking, psychotomimetic drugs are considered to produce symptoms resembling those of schizophrenia, that is, a "model psychosis."

Perhaps the best known of these agents is lysergic acid diethylamide (LSD-25), the structure of which is shown in figure 7. This drug, closely

related to other ergot alkaloids, was accidentally discovered to have a strong effect on mental functions.<sup>28</sup> Among effects commonly described from taking such minute amounts of the drug as 100  $\mu$ g. or less are anxiety, visual hallucinations, paranoid delusions, feelings of unreality, spatial distortions, increased perceptual awareness, dysesthesias, mood changes, trembling, and other signs of sympathetic overactivity.

A more ancient drug is trimethoxy phenyl ethylamine (mescaline). This drug, which occurs naturally in the peyote plant and is used ceremonially by Indians in New Mexico, has properties similar to those described for LSD-25.<sup>29</sup> Chemically, it closely resembles naturally occurring sympathetic amines such as epinephrine and norepinephrine. A degradation product

#### PSYCHOTOMIMETIC DRUGS

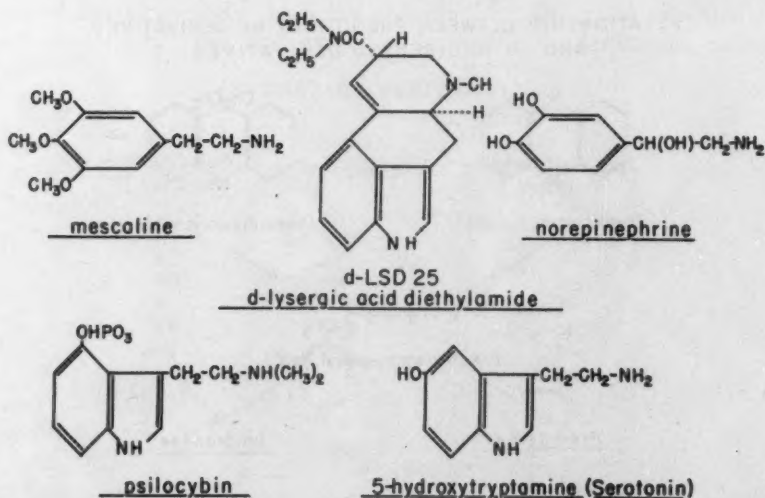


FIG. 7.

of epinephrine, adrenochrome, has a structure somewhat similar to mescaline, and is said to have similar psychic effects. Endogenous production of such materials has been suggested as a possible explanation for the mechanism for symptoms of schizophrenia.

Psilocybin has been recently discovered as a psychotomimetic. This agent is the active principle of mushrooms used ceremonially by Mexican Indians for production of religious trances. The chemical structure of psilocybin is now known, and, as can be seen in figure 10, it resembles serotonin. The latter substance, which occurs freely in the brain, is believed to play a significant role as a neurohormone. The close chemical relationship between psilocybin and serotonin suggests that the former material may compete with the latter. If such proves to be the case, then

the position of serotonin as a neurohormone would be considerably strengthened, as would the hypothesis that disturbances in its function are important in psychoses.

The three agents described above are predominantly central sympathetic stimulants, presumably inducing abnormal mental states by this action. However, a similar condition can be produced by agents which are centrally parasympatholytic. For instance, it has long been known that some belladonna alkaloids, such as scopolamine, may produce abnormal mental states. Similar types of reactions have occurred with synthetic anticholinergic agents, such as benactyzine. A new group of centrally acting parasympatholytic agents, esters of benzilic acid, has been described.<sup>30</sup> Psychic effects from these agents are somewhat similar to those of the others, although auditory hallucinations and postdrug euphoria are said to be more common. Another agent which has been used ceremonially is iboguaiue, obtained from the root of a plant. This material, an indole derivative the structure of which has not been established, also has mental effects similar to those of the other psychotomimetics.

Despite extensive investigation of these drugs, especially LSD-25, the exact mode of action is still not clear.<sup>31, 32</sup> One hypothesis is that LSD-25 blocks serotonin, and that this is the mechanism for its action. Nevertheless, the evidence is conflicting. Possibly no single pharmacologic action may explain adequately the extremely potent effects of LSD-25. For the most part these agents have been used for producing "model psychoses," the hope being that their study may elucidate the pathophysiologic mechanisms of mental disorders. Attempts to use these drugs for facilitating psychotherapy have been made for some time, and interest in this possible use still persists.

#### DISCUSSION

Our look at drugs used in the last 20 years for treating emotional disorders should confirm the fact that such use antedated tranquilizing agents and the current enthusiasm. Needless to say, few of the older drugs were as therapeutically effective as the newer agents. The older drugs are now rarely used, most drug therapists preferring the new agents.

The enthusiasm with which the phenothiazine derivatives and Rauwolfia alkaloids were welcomed as treatments for emotional disorders has waned only slightly. Five years after their introduction in this country they are still regarded as highly useful in treating emotional disorders. These drugs, especially the phenothiazine derivatives, have become a basic part of psychiatric treatment in most psychiatric hospitals, and possibly the most important single treatment for patients with major psychoses, such as schizophrenic reactions. The greatest opposition to them has been by physicians treating patients with less severe forms of emotional disturbance and relying extensively on psychotherapeutic technics. Even more im-

portant than the therapeutic effect of tranquilizing drugs, elucidation of their modes of action may do much to explain the neural mechanisms of emotional expression.

It is questionable whether any of the newer phenothiazine derivatives offer substantially greater therapeutic effect than chlorpromazine. While some of the newer derivatives have more specific kinds of indications, such as for withdrawn and regressed patients, or less allergic complications, the gains are minor. As far as tranquilizers other than the phenothiazine derivatives and Rauwolfia alkaloids are concerned, one enters an area of considerable dispute. Here the break with the past is not so great. The step from mephenesin to meprobamate merely represents improvement of an older agent. Meprobamate is definitely an improvement as far as treatment of emotional disorders is concerned. Whether it has any distinct superiority over more conventional sedatives is still debated. Similarly, the diphenylmethane derivatives were represented earlier by some of the antihistaminics. Many antihistaminics are now being merchandised as tranquilizers, some being sold over-the-counter. The diphenylmethane derivatives with anticholinergic and stimulant actions, while emphasizing the diversity of this particular class of drugs, have never achieved wide acceptance in the treatment of emotional disorders.

Although experienced clinicians had little doubt about the efficacy of tranquilizers at a comparable stage of development, much conflicting opinion exists regarding the antidepressants. Much difficulty stems from the fact that depression has a high rate of spontaneous remission. Nevertheless, these drugs may have definite and specific therapeutic effects in some depressed patients.

The fact that the hydrazides strongly inhibit the enzyme, mono-amine oxidase, has suggested this as a mode of action. Mono-amine oxidase is important in the degradation of central nervous system amines such as epinephrine, norepinephrine and serotonin. Much of the central nervous system effect of hydrazides is thought to be due to their ability to inhibit this enzyme, with resultant accumulation of the amines. Very likely other pharmacologic effects of these drugs are important besides enzymatic inhibition. The simple chemical structure of hydrazides has led to a great deal of investigation of compounds with related structures, with a rapid expansion in the number of these derivatives.

Investigation of the psychotomimetic drugs has been proceeding at an ever increasing pace since the introduction of the tranquilizers. Both animal and clinical work with these agents has led to much contradictory evidence. In clinical studies especially, one is struck by the lack of any consistent responses. Far more perturbing have been the inferences drawn by some of the experimenters, inferences often abounding with semantic and logical errors. For instance, psychotomimetics are often referred to as "hallucinogenic" drugs, implying the production of hallucinations. What is usually

meant is that subjects given these agents have optical illusions which are seldom if ever confused with reality (give or take an odd subject). The word "hallucination," on the other hand, implies confusion between what is perceived and what exists in the real world. While visual hallucinations are common in various toxic deliria (such as delirium tremens), they are uncommon in schizophrenics. Indeed, the most frequent hallucination of schizophrenics is auditory, usually with paranoid content. Because of these and other differences, the relevance of drug-induced abnormal mental states to schizophrenia has been questioned by many investigators.

Nonetheless, the error of assuming that these drugs replicate schizophrenia has been commonly made. A further extension of this illogic has been to search for an agent which blocks the drug effect, assuming that it will also ameliorate schizophrenia. Although a number of such blocking agents for LSD-25 have been described, only chlorpromazine has been found to have a therapeutic effect.<sup>33</sup> Some of the blocking agents have been older agents, such as methamphetamine and barbiturates, while others have been therapeutically useless. Despite these cautions regarding the limitations of psychotomimetic drugs, they still may be most useful for further pharmacologic investigation. Future research with them may prove fruitful in explaining some physiologic mechanisms of disturbed mental functions.

The success of psychopharmacologic agents in treating emotional disorders has led to the belief that only more (or more powerful) drugs are needed to solve the enigma of mental illness. It should be emphasized that little, if any, hard fact supports such wild speculation. As yet, we have no convincing evidence that the drugs do more than control abnormal behavior and lessen the symptoms of psychopathology. Big as this achievement has been, it is far from enough. There is no drug yet known which will remove a patient from a stressful environment or influence human behavior and thought as much as persons and ideas do. Insight into the causes of emotional illness will be obtained more readily if all investigators keep constantly in mind both the sociopsychologic and the biologic factors involved.

#### SUMMARY AND CONCLUSIONS

The present crop of drugs for treating emotional illnesses follows a long list of previous pharmacologic treatments. The chief difference is that some of the newer agents are far more useful than any past drugs. The three broad categories of psychopharmacologic agents are: (1) tranquilizers, (2) antidepressants, and (3) psychotomimetics. As with previous drugs, the aims of therapy are similar: calming disturbed behavior, relieving symptoms of mental depression, and facilitating psychotherapy.

Tranquilizing drugs fall mainly into four groups, though rapidly increasing in numbers. Phenothiazine derivatives and Rauwolfia alkaloids are new types of compounds, both in chemical structure and in pharmacologic actions. Diphenylmethane and glycerol derivatives are related to

previous drugs and differ in many respects from the other two groups. While tranquilizing drugs have proved to be effective for a wide variety of emotional illnesses, most importantly the schizophrenic reactions, their utility is limited.

A revival of interest in the hydrazide derivatives has started a search for other agents with antidepressant properties. A new series of iminodibenzyl derivatives may also prove promising. Therapeutic results of antidepressant agents are still not fully assessed, in part because of the generally favorable course of mental depressions.

The psychotomimetic drugs have been used chiefly as tools for exploration of the mind (often with some notoriety), as well as for facilitating psychotherapy. The relevance of the abnormal mental states produced by them to schizophrenia has been challenged by many investigators. Just how useful these drugs will be as experimental tools remains to be determined.

#### ADDENDUM

Only generic names for drugs are used in this paper. The corresponding trade-names are indicated in parentheses in the following alphabetic listing of the generic names: Adiphenine (Trasentine), amphetamine (Dexedrine, Benzedrine), azacyclonol (Frenquel), benactyzine (Suavatil), b-phenylisopropylhydrazine (Catron), chlorpromazine (Thorazine), deanol (Deaner), deserpidine (Harmony), methamphetamine (Desoxyn), diphenhydramine (Benadryl), diphenylhydantoin (Dilantin), ergotamine (Gynergen), fluphenazine (Prolixin), hydroxyzine (Atarax), imipramine (Tofranil), iproniazid (Marsilid), mepazine (Pacatal), mephensin (Tolserol), meprobamate (Miltown, Equanil), methapyrilene (Thenylene), methylparafynol (Dormison), nikethamide (Coramine), pentylenetetrazol (Metrazol), perphenazine (Trilafon), phenaglycodol (Ultran), pipradrol (Meratran), prochlorperazine (Compazine), promazine (Sparine), promethazine (Phenergan), rescinnamine (Moderil), reserpine (Serpasil), syrosingopine (Singoserp), thiopropazate (Dartal), thioridazine (Mellaril), trifluoperazine (Stelazine), triflupromazine (Vesprin), trimethadione (Tri-dione), tripeleminamine (Pyr benzamine).

#### ACKNOWLEDGMENT

The author thanks Miss Kay Hyde for helping to prepare the figures.

#### SUMMARY IN INTERLINGUA

Le utilisation de drogas in le tractamento de morbos emotional precede per multe annos le currente entusiasmo pro ille forma de therapia. In le passate 20 annos, un grande numero e un grande varietate de agentes pharmacologic esseva usate pro calmar le comportamento disturbate del patiente, pro alleviar le symptommas de depression mental in ille, e pro facilitar in general le application de mesuras psychotherapeutic.

Le formas de tractamento jam ancian include le uso de depressores del systema nervose central, como per exemplo le agentes anti-convulsori e myorelaxante. Le induction de convulsiones e de reactiones simile a tales esseva effectuate. Stimulatores del systema nervose central, a vices in combination con sedativos, esseva in uso. Drogas psychomimetic, vitaminas, hormones, e varie altere pharmacos esseva essayate.

Al tempore presente, tres classes de drogas se trova in uso in le studio e le tractamento de disordines emotional. Illos es (1) tranquillisantes, (2) anti-depressionales, e (3) psychomimeticos. Le tranquillisantes reguardate como le plus efficace es derivatos de phenothiazina e alcaloides de Rauwolfia. Le phenothiazinas es possiblementemente le plus importante agente therapeutic in le psychoses major. Derivatos

de diphenylmethano e glycerol, que es plus intimamente relationate con le agentes traditional, se trova minus generalmente appreciate como efficace tranquillisantes. Derivatos de hydrazido e un nove serie de derivatos de iminodibenzyl se trova sub investigation como possibile agentes anti-depressional. Le utilitate de drogas psychomimetic como instrumentos experimental es ancora questionabile, specialmente con respecto al question del pertinentia del anormal status mental evocate per illos ab le puncto de vista del studio del reacciones schizophrenic.

Drogas, specialmente le plus recente agentes, es demonstratemente capace a stabilisar le comportamento anormal del pacientes e a reducer le symptomatologia de lor psychopathologia. Drogas non effectua le protection del paciente contra le effectos de un ambiente adverse. Illos non exerce un influencia comparabile al influencia de esseres human e de ideas.

#### BIBLIOGRAPHY

1. Kubanek, J. L., and Rowell, R. C.: The use of Dilantin in the treatment of psychotic patients unresponsive to other treatment, *Dis. Nerv. System* 7: 47-50, 1946.
2. Samuels, A. S.: Phenergan in treatment of psychiatric patients, *Dis. Nerv. System* 18: 183-188, 1957.
3. Schlan, L. S., and Unna, K. R.: Some effects of Myanesin in psychiatric patients, *J. A. M. A.* 104: 672-673, 1949.
4. Frank, J. A., and McGraw, R. B.: Carbon dioxide therapy: a clinical evaluation of 200 patients, *J. Nerv. and Ment. Dis.* 123: 563-567, 1956.
5. Sackler, R. R., Sackler, M. D., van Ophuijsen, H. W., Tui, C., and Sackler, A. M.: An appraisal of the current status of histamine biochemotherapy in psychiatry and the theoretical significance of its effects. *Endocrinologic orientation to psychiatric disorders*, *J. Clin. and Exper. Psychopath.* 12: 5-13, 1951.
6. Forrer, G. R.: Symposium on atropine toxicity therapy. History and future research, *J. Nerv. and Ment. Dis.* 124: 256-281, 1956.
7. De M. Rudolf, G.: The treatment of depression with desoxyephedrine (Methedrine), *J. Ment. Sc.* 95: 920-929, 1949.
8. Davidoff, E., and Goodstone, G. L.: The amphetamine-barbiturate therapy in psychiatric conditions, *Psychiatric Quart.* 16: 541-548, 1942.
9. Parker, D. S., and Wrigley, F.: Synthetic cannabis preparations in psychiatry: Synhexyl, *J. Ment. Sc.* 96: 276-279, 1950.
10. Levine, J., Rinkel, M., and Greenblatt, M.: Psychological and physiological effects of intravenous Pervitin, *Am. J. Psychiat.* 105: 429-434, 1948.
11. Wedge, B., and Moulton, M.: A method of pharmacologic facilitation of psychiatric investigation, *J. Nerv. and Ment. Dis.* 3: 116-121, 1950.
12. Bursch, A. K., and Johnson, W. C.: LSD-25 as an aid in psychotherapy. Preliminary report of a new drug, *Dis. Nerv. System* 11: 241-243, 1950.
13. Rockwell, F. V., and Diethelm, O.: Dibenamine therapy in certain psychopathologic syndromes, *Tr. Am. Neurol. A.* 73: 127-131, 1948.
14. Kral, V. A., and Krauser, W. G.: Psychiatric experiences with Plexonal, *Canad. M. A. J.* 70: 453-455, 1954.
15. Chlorpromazine and mental health, Symposium, 1955, Lea and Febiger, Philadelphia.
16. Miner, R. W., editor: Symposium: Reserpine in the treatment of neuropsychiatric, neurological, and related clinical conditions, *Ann. New York Acad. Sc.* 61: 1-280, 1955.
17. St. Whitelock, O. V., editor: Symposium: Meprobamate and other agents used in mental disturbances, *Ann. New York Acad. Sc.* 67: 671-894, 1957.
18. Himwich, H. E.: Psychopharmacologic drugs, *Science* 127: 59-72, 1958.
19. Hollister, L. E.: The present status of tranquilizing drugs, *California Med.* 89: 1-6, 1958.

20. Hollister, L. E.: Complications from the use of tranquilizing drugs, *New England J. Med.* **257**: 170-177, 1957.
21. Wikler, A.: The relation of psychiatry to pharmacology, American Society for Pharmacology and Experimental Therapeutics, 1957, The Williams and Wilkins Co., Baltimore.
22. Smith, J. A.: The use of the isopropyl derivative of isonicotinylhydrazine (Marsilid) in the treatment of mental disease; a preliminary report, *Am. Pract. and Digest Treat.* **4**: 519-520, 1953.
23. Sackler, M., editor: Symposium on the biochemical and clinical aspects of Marsilid and other monoamine oxidase inhibitors, *J. Clin. and Exper. Psychopath.* **19** (supplement 1): 1-186, 1958.
24. St. Whitelock, O. V.: Symposium on monoamine oxidase inhibitors, *Ann. New York Acad. Sc.*, in press.
25. Kuhn, R.: The treatment of depressive states with an iminodibenzyl derivative (G 22355), *Schweiz. med. Wchnschr.* **87**: 1135-1140, 1957.
26. Lehmann, H. E., Cahn, C. H., and deVerteuil, R. L.: The treatment of depressive conditions with imipramine (G 22355), *Canad. Psychiat. A. J.* **3**: 155-164, 1958.
27. Lemere, F., and Lasater, J. H.: Deanol (Deaner) a new cerebral stimulant for the treatment of neurasthenia and mild depression: a preliminary report, *Am. J. Psychiat.* **114**: 655-656, 1958.
28. Stoll, W. A.: LSD, a hallucinatory agent from the ergot group, *Schweiz. Arch. Neurol. u. Psychiat.* **60**: 1-45, 1947.
29. Berlin, L., Guthrie, T., Weider, A., Goodell, H., and Wolff, H. G.: Studies in human cerebral function. The effects of mescaline and lysergic acid on cerebral processes pertinent to creative activity, *J. Nerv. and Ment. Dis.* **122**: 407-491, 1955.
30. Ostfeld, A. M., Visotsky, H., Abood, L., and Lebovitz, B. Z.: Studies with a new hallucinogen. Some dosage-response tests for JB-318, *Arch. Neurol. and Psychiat.* **81**: 256-263, 1959.
31. St. Whitelock, O. V., editor: Symposium. Pharmacology of psychotomimetic and psychotherapeutic drugs, *Ann. New York Acad. Sc.* **66**: 417-840, 1957.
32. Koelle, G. B.: The pharmacology of mescaline and d-lysergic acid diethylamide (LSD), *New England J. Med.* **258**: 25-32, 1958.
33. Elder, J. T., Gogerty, J. H., and Dille, J. M.: Survey of d-lysergic acid diethylamide (LSD) antagonists, *Federation Proc.* **16**: 293, 1957.

## MARFAN'S SYNDROME AND THE WEILL-MARCHESANI SYNDROME IN THE S. FAMILY \*

By DORRANCE BOWERS, M.D., M.S. (Med.), F.R.C.P. (C),  
*Kelowna, British Columbia, Canada*

"... A large number of abnormal conditions are known to be inherited in man. . . . Few, if any . . . are determined by a known genetic mechanism in a known way. . . . Such meagre information as we have comes from the efforts of people who found themselves interested in the subject and seized what small opportunity they could to make observations which they thought would be of some value."—Boyd<sup>1</sup>

### INTRODUCTION

ABOUT the middle of the nineteenth century a young couple emigrated to Canada from Germany.<sup>2</sup> They brought with them a curse which, to the present time, has caused serious visual handicap, early or sudden death, and bitter heartache through the six successive generations of their descendants. This affliction carries the innocuous designation, Marfan's syndrome. It is of additional interest that two of their descendants have demonstrated features suggestive of the Weill-Marchesani syndrome, and that another descendant died as a result of the congenital cardiac malformations known as the tetralogy of Fallot.

In this paper, the historical evolution of Marfan's syndrome and some of the speculation concerning its etiology will be reviewed briefly as a preface to the presentation of data derived from these descendants.

In 1896 Marfan,<sup>3</sup> a Parisian pediatrician, described a single patient with long, slender extremities and a rather marked degree of dolichocephaly. He stated specifically that his patient's eyes were normal. He proposed the name *Dolichostenomelia*, to refer to the gracile limbs. In 1902 Achard<sup>4</sup> reported a similar patient, and coined the term *Arachnodactyly* to emphasize the spidery extremities. One of the first reports to associate dislocated ocular lenses with arachnodactyly was published in 1914 by Boerger.<sup>5</sup> This interesting combination of anomalies became well-documented in the ophthalmologic literature and, in spite of the deviation from the condition described by Marfan, was frequently referred to as Marfan's syndrome or Marfan's symptom-complex. Although many of the early reports suggested that this syndrome was hereditary in transmission, the families described by

\* Received for publication May 22, 1959.

From the Knox Clinic and Kelowna General Hospital, Kelowna, British Columbia, Canada.

Requests for reprints should be addressed to Dorrance Bowers, M.D., Knox Clinic, 426 Lawrence Avenue, Kelowna, British Columbia, Canada.

Weve<sup>8</sup> in 1931 were the first to substantiate this impression. Further reports confirmed the hereditary nature of the syndrome, indicating that it was transmitted as a dominant characteristic. (It must be acknowledged that a hereditary background cannot be established in every case. In McKusick's<sup>7</sup> experience, "no more than 15%" of all cases occurred as a result of new mutation.) It remained for Baer, Taussig, and Oppenheimer<sup>9</sup> and for Etter and Glover<sup>10</sup> in 1943 to direct attention to the characteristic cardiovascular involvement associated with this syndrome, namely, degeneration of the medial layer of the aortic wall. Prior to 1943, Weve<sup>8</sup> had reported a patient (his first case) with dislocated lenses who had an operation for an aortic aneurysm, and Weill<sup>11</sup> had presented clinical and pathologic data from a patient (his second autopsy case and his third clinical case) with dislocated lenses and aneurysmal dilatation of the aortic sinuses.

Before the pathogenesis of Marfan's syndrome is considered, it should be pointed out that the familial, ocular and skeletal manifestations of this syndrome had been clearly described by Williams,<sup>12</sup> an ophthalmologist in Cincinnati, in 1876. He reported dislocation of the ocular lenses in two pairs of siblings. From the data presented, it is probable that the second pair had Marfan's syndrome. Mary J. had a divergent squint, iridodonesis, bilateral upward dislocation of the lenses, and a detachment of the retina in her right eye. Her brother, Marcus J., "large and loose-jointed like his sister" also had a divergent squint and bilateral upward dislocation of the lenses. "The father's eyes were like theirs, but their mother and only brother had good eyes."

The mechanism responsible for the abnormalities collectively known as Marfan's syndrome remains as obscure now as in 1896. The following suggestions concerning the etiology of this syndrome are of interest. First, in his original report, Marfan<sup>8</sup> pointed out that, during the first month of her pregnancy, his patient's mother had been strongly impressed by the sight of a burned man. Second, Méry and Babonneix<sup>13</sup> reported Marfan's patient again at a later date, contrasting her deformity with the deformity of achondroplasia. In this regard, it is interesting that achondroplasia is also inherited as a dominant characteristic. Third, it has been widely accepted through the years that the fundamental defect in Marfan's syndrome rests in mesodermal or connective tissues. The ectodermal origin of the ocular lens constitutes a serious objection to this explanation of the pathogenesis of this syndrome. However, this objection loses its significance if it is agreed that the abnormality of the lens is secondary to dysplasia of the mesodermal ciliary body. Finally, the recent observation by Ponseti and Shepard<sup>14</sup> of kyphoscoliosis, periosteal new bone formation, and dissecting aneurysms of the aorta in rats fed diets containing 50% sweet pea seeds may perhaps be related to the pathogenesis of Marfan's syndrome. It will be apparent that there is more speculation than information available concerning the etiology of this symptom-complex.

The patients previously reported from Canada as examples of Marfan's syndrome by Patterson<sup>15</sup> in 1933 and by Gibson<sup>16</sup> in 1956 had the skeletal stigmata without the ocular or cardiovascular abnormalities. Evidence regarding the familial nature of the skeletal anomalies was noted in the case reports of two of the four patients presented by Gibson,<sup>16</sup> who kindly made the pedigree data<sup>17</sup> from these two cases available to the author. Two Canadian patients<sup>18,19</sup> who required surgical treatment for aortic complications of Marfan's syndrome have recently been reported. Examples of Marfan's syndrome in three other Canadian families have also come to the author's attention. It has not been possible to establish any familial relationship between these other Canadian cases and the cases to be described in this paper.

A number of families, each containing multiple cases of Marfan's syndrome, have been described in the medical literature. Lutman and Neel<sup>20</sup> reported 17 cases in three generations of the E. family. McKusick<sup>7</sup> illustrated (his figure 9A) a Negro family pedigree with 10 cases in four generations. Recently, Wilson<sup>21</sup> described a family in which eight cases had occurred in three generations. The S. family to be described in this paper is believed to have contained at least 33 affected\* members in six generations. To the author's knowledge, there are more affected members in this family than in any other family thus far reported. The skeletal, ocular, cardiovascular and hereditary characteristics of Marfan's syndrome are all well exemplified in the S. family. Brief descriptions of this family have been published elsewhere.<sup>22</sup> The family tree of the S. family is shown in figure 1.

#### OBSERVATIONS REGARDING THE S. FAMILY

1. *Nonmedical Data:* I 2a and I 2b are believed to have come to Canada from the Grand Duchy of Baden in Southern Germany. They may have settled temporarily in Wellington County in southern Ontario. Whether or not this is so, they probably took up permanent settlement in Carrick Township in Bruce County in southern Ontario in 1853 or 1854. Although a German migration to Bruce County is mentioned in Robertson's<sup>23</sup> history of this county, the S. family is not specifically cited.

Their daughter II 7 apparently had tuberculosis or asthma, and moved to a farm near North Bay, Ontario. Her descendants have remained as farmers in that area or have moved to Toronto, Ontario, to take up industrial employment.

The sons of I 2a and I 2b remained in Bruce County. Descendants of II 8 are still actively engaged in farming there.

The descendants of II 7 are unknown to the descendants of II 8.

The members of the S. family are Roman Catholics. This fact may help to explain the relatively large size of some of the subfamilies.

As a guide, it should be kept in mind that members of generation VII

\*The word "Affected," as employed in this paper, is defined in the footnote to table 1.

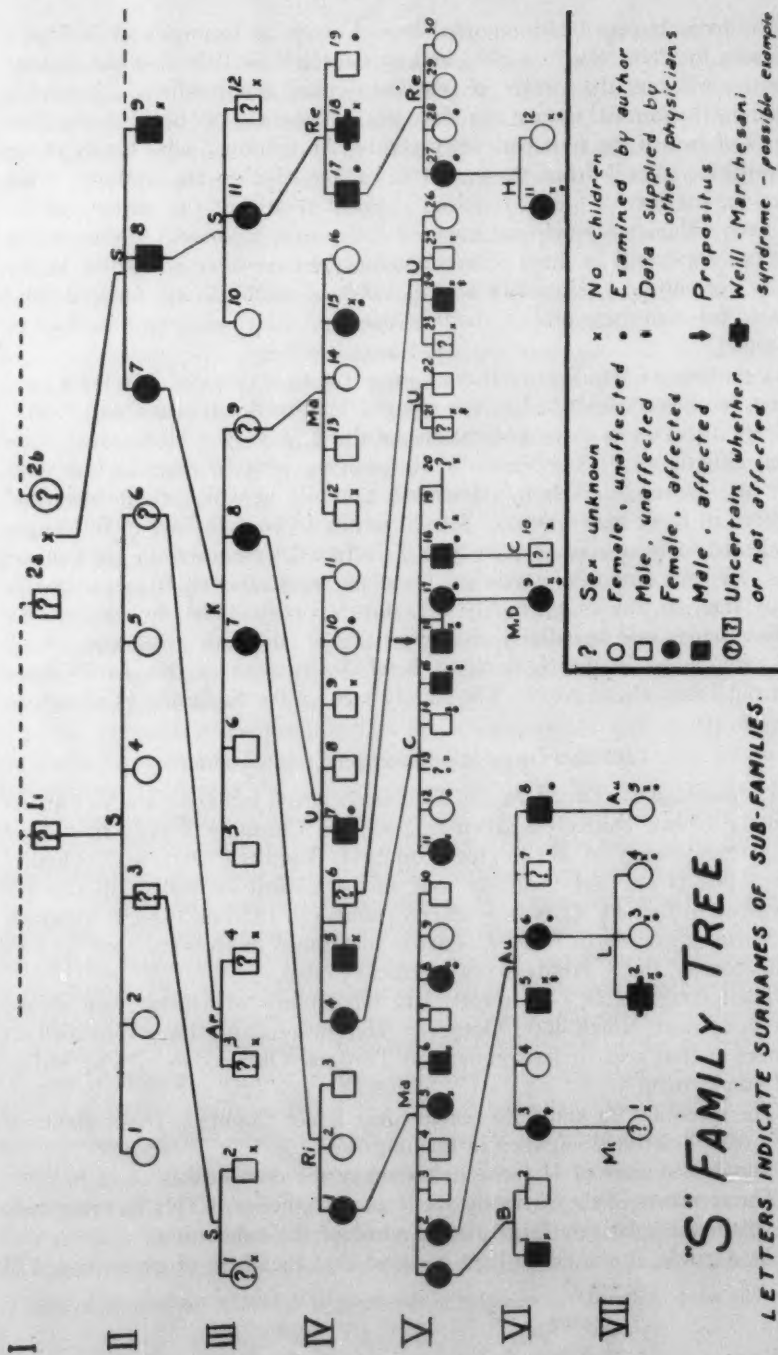


FIG. 1. The family tree of the S. family.

were born after 1950, of generation VI after 1925, of generation V after 1900, of generation IV after 1875, of generation III after 1850, of generation II after 1825, and of generation I after 1800.

2. *Identification of Affected Members:* The family tree is illustrated in figure 1 and annotated in its legend. The information upon which it is based was obtained from interviews and correspondence with members of the family, and their physicians and optometrists.

Frequently, the stigmata of Marfan's syndrome are sufficiently obvious that laymen familiar with these stigmata can recognize them in themselves and in their relatives. It is interesting to relate how infants newly born into this family are examined by other members of the family. The infant is shaken gently in bright sunlight while the pupils of its eyes are carefully examined for the telltale lens dislocations, aptly described as resembling the bubble in a spirit-level. The girl numbered VI 9 was repeatedly examined in this manner by her parents and grandparents during infancy. The lens dislocations were first recognized when the girl was three months old. In the absence of lens dislocations it may be difficult, even for experienced observers, to be confident regarding the diagnosis of Marfan's syndrome. The diagnosis of Marfan's syndrome was doubtful in the cases of certain members of this family. These doubtful cases are clearly identified in figure 1.

3. *Case Reports:* Each case has been classified depending upon the sources of information concerning it. The specifications of each category are presented in detail in the footnote to table 1.

FIG. 1. The family tree of the S. family. The members of each subfamily have not been numbered in the order of descending ages, because reliable data regarding birth dates were not always obtainable. The numbering is arbitrary.

To conserve space, the descendants of unaffected members have been omitted if there has been no evidence of the occurrence of Marfan's syndrome or the Weill-Marchesani syndrome in these descendants. This has resulted in eliminating more than 200 descendants from the family tree.

The dotted lines indicate probable lines of descent. In all genealogic research, the only absolute proof of descent is visualization of the umbilical cord. Other evidences of descent are presumptive to varying degrees. The dotted lines in this family tree indicate that there has been no assured statement by members of the family regarding the relationship between individuals whose symbols are joined by dotted lines. The relationship indicated by the dotted lines has been specified by the author after considering the available pertinent data.

The capital letters indicate the surnames of the various subfamilies. The only surviving member of the family who carries the surname S. is III 2. He has no children, so that this surname will drop out of the family. Nevertheless, for want of a better designation, the author has chosen to refer to the entire family as the S. family.

The apparent 100% involvement of the children of I 2a and I 2b may be: (1) an artifact due to lack of knowledge regarding unaffected siblings; (2) a chance occurrence—if only the mother was affected (see text for additional comment), there is one chance in eight that she might have had three affected siblings; (3) theoretically at least, the result of the mating of two affected individuals; according to McKusick,<sup>7</sup> there is no documented example of such a mating in the medical literature; or (4) due to an even more remote possibility, namely, three new mutations.

There has been no close intermarriage in this family, although subfamilies IV 12 to IV 16 and V 1 to V 10 did have the same surnames. The surname of subfamily IV 1 to IV 3 had the same pronunciation as the surname of subfamilies IV 17 to IV 19 and V 27 to V 30 but was spelled differently.

*Confirmed Cases, Living and Dead:*

*Case IV 7:* This 66 year old farmer had bilateral iridodonesis (tremulous movements of the iris pathognomonic of subluxation, dislocation, or absence of the lens) and lens dislocations. His head was dolichocephalic. His limbs were long and slender (figure 2). He had a marked funnel-chest deformity and a moderate upper dorsal kyphosis. There was webbing between his fourth and fifth toes. Clinical examination of his cardiovascular system disclosed no noteworthy abnormalities.

*Case IV 15:* This 61 year old widow possessed a remarkable knowledge of her family. Although she was not the first member of the family to come to the author's attention, this study could not have attained these proportions without her cooperation. She had had bilateral dislocations of the ocular lenses. The lenses had been removed surgically when she was 19 years of age. She had a divergent squint. Her skull was dolichocephalic. Her extremities were long and thin. Her case is



FIG. 2. IV 7. This man is a 66 year old farmer. Note the divergent squint, dolichocephaly and arachnodactyly. He still performs strenuous physical work. Photograph by the author.

of particular interest because she is convinced that neither of her parents had Marfan's syndrome.

*Case IV 17:* This 54 year old farmer had had an ancient injury to his right eye, with a resulting corneal opacity. Although he attributed his visual handicap to this injury, it was obvious, after questioning him, that he had had poor vision all his life. Iridodonesis and dislocation of the ocular lens could be demonstrated in his left eye. He had a divergent squint. He was dolichocephalic; his extremities were long and slender; he had a dorsal kyphosis. There was no clinical evidence of cardiovascular disease.

*Case V 8:* This 47 year old housewife was skeptical of the author's motives in studying the family, and limited her cooperation to posing for a snapshot. She wore thick corrective lenses because of a lifelong visual handicap, the exact nature of which she kept secret. The appearance of the corrective lenses suggested that her eyes were functionally aphakic. Her skull was dolichocephalic. Her extremities were normal in length.

*Case V 15:* The data concerning this man were made available to the author by the Medical Records Departments of the Toronto General Hospital<sup>24</sup> and of the University of Alberta Hospital.<sup>25</sup>

He had had bilateral ocular lens dislocations and had required extraction of the lens from the left eye following the development of secondary glaucoma. He was dolichocephalic, and had kyphoscoliosis of the thoracic spine. He had long, slender fingers and toes. The following evidence was interpreted to indicate that he had moderately severe aortic valvular insufficiency: blood pressure, 120/40 mm. of Hg; a grade 3 left parasternal and apical diastolic murmur; and left ventricular hypertrophy on both fluoroscopic and electrocardiographic examination.

Routine serologic tests were repeatedly positive for syphilis, as was a *Treponema pallidum* immobilization test.

He died at his home in 1956 at the age of 35, apparently as a result of intractable cardiac failure. No postmortem examination was carried out.

*Case V 16:* This 34 year old janitor has required medical attention on many occasions for severe pains in his neck, chest and abdomen. These pains have had certain constant characteristics, namely, that they have been aggravated by extension of the spine, and have been reduced in intensity if he sat hunched forward. Although the pains have been sufficiently severe to require opiates by hypodermic injection, there has been no question of an addiction problem, because the pains have been separated by intervals of weeks or even months. Routine radiographic studies have been unrewarding in determining the cause of these pains. It has been suspected that the pains have been caused by minor aortic dissections.

This patient presented the classic physical characteristics of Marfan's syndrome, the dolichocephalic skull, the high, arched palate, and the gracile extremities. He had had bilateral lens dislocations. As a complication of repeated ophthalmologic surgery, his left eye had required enucleation; limited vision remained in his right eye. He had a persistent low grade hypertension of 140/100 mm. of Hg. His electrocardiogram showed nonspecific T wave abnormalities.

At his own request, he had undergone an operative sterilization procedure while under the care of another physician.

*Case V 17:* The twin sister of the above described patient presented herself for examination because of occasional transient episodes of loss of consciousness. These attacks were, at times, preceded by what she described as a "flip-flopping" of her heart. The loss of consciousness was not accompanied by convulsive movements or incontinence, its maximal duration was less than five minutes, and the patient was able to resume her customary activities as soon as consciousness returned.

She had a dolichocephalic skull, vaulted palate and spidery extremities. She considered her fifth fingers bilaterally to be "abnormally short." (Another interpretation of the discrepancy in the lengths of her fingers is to consider the fifth fingers normal in length and the remaining fingers abnormally long. McKusick<sup>7</sup> has described shortening of the fifth fingers due to a flexion deformity (clinodactyly or camptodactyly) in patients with Marfan's syndrome. In this patient, the fifth fingers were not flexed or deformed, merely shortened.)

Her eyes showed iridodonesis, and she had bilateral lens dislocations. She had sustained a recent retinal detachment in her left eye. Her ophthalmic surgeon told her that striking her head lightly during one of her syncopal attacks may have precipitated the retinal detachment.

No abnormality of her cardiovascular system was found. Her blood pressure, chest roentgenogram and electrocardiogram were normal. The explanation for her syncopal attacks was not determined.

At her own request, she had previously had an operative sterilization while under the care of another physician following the birth of her daughter VI 9.

*Case V 18:* This 27 year old musician and television entertainer had a dolichocephalic skull, high, narrow palate, long, slender extremities, and particularly prominent tibial tubercles. No abnormality of his cardiovascular system was noted. He had severe myopia but no lens dislocations.

*Case V 24:* The author has not had the opportunity of meeting this man but has been able to examine his photograph and to review the findings of his optometrist.<sup>26</sup> This member of the family is approximately 30 years old; he has a dolichocephalic skull, long, slender extremities, and bilateral dislocation of the ocular lenses.

*Case V 27:* This 34 year old housewife had no complaints regarding her health. She had bilateral iridodonesis and lens dislocations. She had a divergent squint. She had marked dolichocephaly and striking arachnodactyly (figure 3). There was no clinical evidence of cardiovascular disease. She resembled V 17 so closely that she might have been thought to be her sister; actually, she was a distant cousin.



FIG. 3. V 27. This 34 year old housewife had no knowledge that she had Marfan's syndrome. The light reflex from her thick lenses has been employed to conceal her identity. Note the dolichocephaly and arachnodactyly. Photograph by the author.

*Case VI 3:* Between the years of 1933 and 1942, this woman attended the Ontario School for the Blind in Brantford, Ontario. The following information was provided to the author by the school authorities.<sup>27</sup> She was "husky and well built"; she had dislocated ocular lenses and severe myopia.

*Case VI 5:* Details concerning this patient were supplied by his ophthalmologist, Dr. O. B. Richardson.<sup>28</sup> The patient had dislocated ocular lenses but "none of the other signs of Marfan's syndrome." He had sustained a detachment of the retina in the left eye. He also had been educated at the Ontario School for the Blind.<sup>27</sup>

*Case VI 6:* This 22 year old housewife had known of her bilateral lens dislocations since the age of seven. Her skull was dolichocephalic; her extremities were long and slender. She was obese.

*Case VI 8:* This 29 year old man was able to carry out the strenuous physical tasks of a laborer. He had bilateral iridodonesis and lens dislocations, together with a divergent squint. His head was dolichocephalic; his extremities were normal in length.

*Case VI 9:* This 11 year old girl had no complaints regarding her health. Her skull was dolichocephalic; her extremities were long and slender (figure 4). She had bilateral iridodonesis and lens dislocations. No cardiovascular abnormalities were apparent.

*Case VI 11:* This four year old girl had a divergent squint, bilateral iridodonesis and lens dislocations. She was dolichocephalic. Her extremities appeared to be normal in length. There was no clinical evidence of cardiovascular disease.

*Case VII 2:* This three year old boy was the youngest affected member of the family to be examined by the author. The boy's vision had been defective since infancy. His mother had noticed the bilateral iridodonesis but had failed to detect his bilateral lens dislocations. He had a cube-shaped head; his extremities seemed shorter than normal. These physical characteristics are illustrated in figure 5.



FIG. 4. VI 9. This 11 year old girl has dislocated lenses and gracile extremities. Photograph by the author.



FIG. 5. VII 2. This three year old boy illustrates the brachycephalic skull typical of the Weill-Marchesani syndrome. Note also the thick lenses in his glasses to correct for the gross displacement of his ocular lenses. Photograph by the author.

*Probably Affected Cases, Deceased:* Fifteen individuals, II 7, II 8, II 9 (figure 6), III 7, III 8 (figure 7), III 11, IV 1, IV 4, IV 5, V 1, V 2, V 5, V 6, V 11 and VI 1, all deceased, are believed, on the basis of information from surviving members of the family, to have had Marfan's syndrome.



FIG. 6. II 9. This man was born in 1842 and died in 1908. The daguerreotype from which this photograph was reproduced was made at the time of his wedding, probably about 1870.

His left eye appears to be more prominent than his right. His head is directed slightly toward his right while his eyes are directed toward the photographer, a simple stratagem employed by photographers to mask a squint. The shape of his head is dolichocephalic.

In his later life, he is said to have resembled the present appearance of IV 7 (fig. 2).



FIG. 7. III 8. This lady displays the dolichocephalic skull and the long slender fingers of the patient with Marfan's syndrome. Note also her spectacles and divergent squint.

She was born in 1855, three years before Marfan. Her photograph was reproduced from a family group portrait made about 1905. She died in 1926 from high blood pressure and a "stroke."

A detailed description<sup>29</sup> of the physical characteristics of IV 18 warrants quotation and will be discussed further in this paper.

"He was only about four feet tall with very short legs, one leg shorter than the other. He had short arms and small hands and feet. He had an oblong and rather large head. He never could get glasses strong enough to be able to see, and finally had to quit work on account of his sight."

These 16 individuals, together with the 17 confirmed cases which have been described in detail, form the 33 cases considered affected in this paper.

*Possibly Affected Cases, Living:* To date, the only information regarding the following four members of the family has been obtained from lay observers. It may be possible to secure definitive observations regarding these individuals from physicians or optometrists at a later date. The "possibly

TABLE 1  
Classification of Affected\* Members of the S. Family

Category	Living	Dead	
Confirmed affected cases <sup>a</sup>	16	1	
Probably affected cases: deceased <sup>b</sup>	0	16	
Total <sup>c</sup>	16	17	33
Possibly affected cases <sup>d</sup>	4	14	

\* Throughout this paper, the adjective "Affected" indicates affliction by either Marfan's syndrome or the Weill-Marchesani syndrome.

<sup>a</sup> Observations made by a physician or optometrist indicate that these members of the family were affected. Thirteen of these cases have been examined by the author.

<sup>b</sup> Observations made by lay observers indicate that these members of the family were affected. It has not been possible (nor is it likely to be possible) to secure confirmatory reports from physicians or optometrists concerning these cases.

<sup>c</sup> The conclusions in this paper are based on those members of the family in the categories "confirmed affected cases" and "probably affected cases: deceased." The "possibly affected cases" are mentioned only for the sake of completeness.

<sup>d</sup> Observations made by lay observers suggest that these members of the family may be or may have been affected. Definitive observations by physicians or optometrists concerning living members in this category may be possible in the future.

affected cases, living and deceased" (table 1) are not counted among the affected cases in this paper.

*Case IV 6:* This man, age approximately 50 years, is said to have a weak heart and only one lung.

*Case V 23:* This man, age approximately 30 years, is said to have a congenital abnormality of the iris and subnormal vision.

*Case VI 7:* This man, age approximately 30 years, is said to be very near-sighted and to have extremely long arms and legs.

*Case VI 10:* This infant boy was born in 1957. He is said to have eyes like those of his father V 18, who is affected.

4. *Method of Inheritance:* This family pedigree illustrates the inheritance of a mendelian dominant characteristic.\* There is no evidence of sex linkage, males and females being affected in equal numbers (table 2).

In each generation, approximately 50% of the children of affected individuals are affected. The average number of children born to each affected member of the family now dead was 3.0; the average number of affected children born to each affected member of the family now dead was 1.4 (table 3).

In this family there is a striking difference in the fertility rates of affected males and females. The 14 affected females who survived to the age of 18

TABLE 2  
Sex Incidence of Affected Members

Category	Male	Female	Total
Confirmed cases	9	8	17
Probably affected cases: deceased	6	10	16
Total	15	18	33

TABLE 3  
Fertility of Affected Members of the S. Family

Parents or Potential Parents	Children		
	Affected	Non-affected <sup>a</sup>	Total
Affected members in family (33 in number)	29	38	67
Affected female members surviving to age 18 (14 in number)	26 <sup>b</sup>	28	54
Affected male members surviving to age 18 (14 in number)	3 <sup>b</sup>	10	13
Affected female members now dead (10 in number)	23	24	47
Affected male members now dead (7 in number)	1	2	3

<sup>a</sup> The "possibly affected cases, living and dead" are classed as non-affected in this table.

<sup>b</sup> Note that 26 affected members of the family inherited the stigmata of Marfan's syndrome from their mothers, three from their fathers. The sources of inheritance of Marfan's syndrome in the cases of II 7, II 8, II 9 and IV 15 are not definitely known.

had a total of 54 children; the 14 affected males who survived to the age of 18 had a total of 13 children. (The children of members I 2a and I 2b have been omitted in these calculations; according to family legend, it was I 2b who transmitted Marfan's syndrome; there is no compelling evidence to substantiate this legend.)

This pedigree suggests that this affliction may skip generations. Although it has not been possible to examine all of the critically involved individuals, the following example, where the inherited traits appeared to skip a generation, may be cited: II 7 to III 9 to IV 15. (It is possible that this manner of inheritance may account for some of the reported failures to find evidence of familial involvement in the families of patients with Marfan's

TABLE 4  
Age at Death and Cause of Death of Affected Members

Affected Member (Code)	Age at Death (Years)	Cause of Death (Clinical Diagnosis)
II 7	Approx. 40	Asthma or consumption
II 8	73	Ruptured appendix
II 9	66	Valvular heart disease
III 7	52	Pyorrhea!
III 8	71	Hypertension and stroke
III 11	52	Gall-stones
IV 1	65	Stroke
IV 4	69	Ruptured abdominal aortic aneurysm
IV 5	32	Dissecting aneurysm
IV 18	50	Hypertension and brain tumor
V 1	34	Heart trouble
V 2	53	Heart trouble
V 5	9	Rheumatic fever
V 6	26	Heart attack
V 11	12	Diphtheria
V 15	35	Aortic insufficiency
VI 1	19	Heart attack

syndrome. For example, further study of the pedigree presented by McKusick<sup>7</sup> (in his figure 10C) might demonstrate that the manifested syndrome had skipped generation I.

The high incidence of twin births, IV 5 and IV 6, V 16 and V 17, and V 19 and V 20, cannot pass unremarked. It is difficult to know what significance to attach to this observation. (Identical twins with Marfan's syndrome have recently been reported by Steinberg et al.<sup>80</sup>)

5. *Age at Death of Affected Members:* In the S. family, the affected members frequently died at early ages (table 4). The age at death of II 7 is not accurately known. The average age at the time of death of the 16 affected members for whom the age at death is known was 45 years. The average age at death for the seven affected male members was 43 years, and for the nine affected female members, 46 years.

It should be emphasized that patients with Marfan's syndrome may survive to the sixth and seventh decades. The affected member III 8 (figure 7) reached the age of 71 years; two of the affected members examined by the author, IV 7 and IV 15, have attained the ages of 66 and 61 years, respectively.

6. *Cause of Death of Affected Members:* "Heart trouble" is said to have caused the deaths of at least 11 of 17 affected members (table 4). It is probable that some of the deaths attributed to "heart trouble" were actually caused by aortic disease. Three individuals were reported to have died from aortic disease: IV 4 from a ruptured aneurysm of the abdominal aorta, IV 5 from a dissecting aneurysm, and V 15 from aortic valvular insufficiency.

One member of the family, V 21, who probably did not have Marfan's syndrome, died at the age of 11 years with multiple brain abscesses secondary to the tetralogy of Fallot and bacterial endocarditis.<sup>81</sup>

#### DISCUSSION

Understanding of Marfan's syndrome has been hampered by ignorance of the minimal criteria necessary for its diagnosis. Spidery extremities have been accepted by certain authors as a sufficient condition for this diagnosis. In this connection, McKusick<sup>7</sup> has properly pointed out that long, slender limbs may also occur in eunuchoidism or, as an anthropologic variant, in the Denker Negro. Lens dislocations or aortic medionecrosis, as isolated abnormalities, also should not be accepted as pathognomonic of Marfan's syndrome. At present, the complete triad of skeletal, ocular and aortic abnormalities provides the most substantial basis for the diagnosis of Marfan's syndrome. However, study of families, such as has been presented, confirms the widely accepted belief that incomplete forms of the syndrome, *formes frustes*, do occur; for example, V 18 did not have dislocated lenses, yet his extremities were notably gracile. The question logically arises, How incomplete may the syndrome be? It is not inconceivable that individuals with common "abnormalities," such as isolated dolicho-

cephaly, are, in fact, formes frustes of Marfan's syndrome. The apparent rarity of the syndrome, as presently envisaged, may be an artificial consequence of overly stringent diagnostic criteria.

Many abnormalities have been associated with Marfan's syndrome. The skeletal abnormalities which appear to be frequently associated with this syndrome include: long, slender extremities, pigeon-breast or funnel-chest deformity<sup>32</sup> (attributed to abnormally long ribs, with resulting protrusion or infolding of the sternum), dolichocephaly, high arched palate, scoliosis, kyphosis, and hyperextensibility of the joints. Kilgore<sup>33</sup> associated the following ocular abnormalities with Marfan's syndrome: bilateral dislocation of the ocular lenses, iridodonesis, detachment of the retina, and myopia. McKusick<sup>34</sup> considered the following cardiovascular abnormalities to be

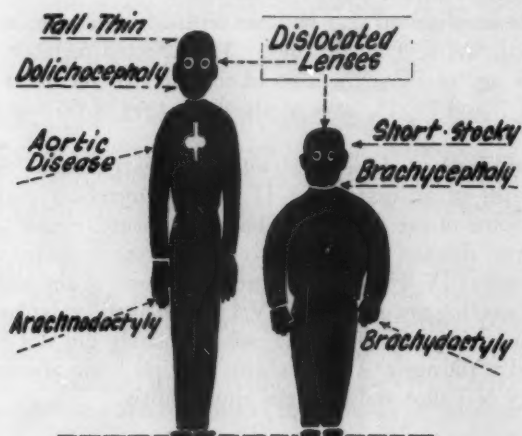


FIG. 8. Caricatures to illustrate the features of Marfan's syndrome and the Weill-Marchesani syndrome. (The latter is on the reader's right.)

frequently associated with Marfan's syndrome: aortic dissection, diffuse aneurysm of the aorta, dilatation of the pulmonary artery, and marginal thickening and nodular excrescences of the cusps of the heart valves.

The affected members of the S. family had a common characteristic which the author has not seen described in the medical literature. This characteristic permitted the author, when telephoning a member of the family, to make a shrewd guess as to whether that individual had Marfan's syndrome. It was observed that affected members had rather high-pitched voices, with a peculiar "cracked-note" quality. Perhaps the high narrow skull with its associated vaulted palate was the determining factor in causing these peculiarities in the voices of affected members.

The association of dislocated ocular lenses with brachymorphism is

known as the Weill-Marchesani syndrome\* (figure 8). Clinically, the patient with this syndrome is short and has a round head and short, pudgy extremities. VII 2 had morphologic features (figure 5) suggestive of the Weill-Marchesani syndrome. The description of the physical characteristics of IV 18 suggests that he too had the Weill-Marchesani syndrome. If these two cases (IV 18 and VII 2) are accepted as examples of the Weill-Marchesani syndrome, it would seem reasonable to assume that the morphologic differences between Marfan's syndrome and the Weill-Marchesani syndrome are of insufficient importance to justify any genetic distinction between the two.

The incidences of the major stigmata of Marfan's syndrome in the medically examined affected members of the S. family may be expressed in several ways:

1. *In the 17 cases:* Dislocation of the ocular lenses occurred in 94% of the cases, while clinical evidence of aortic disease was recognized in only 15%; dolichocephaly occurred in 94%, dolichostenomelia in 70%.

2. *For each individual case:* The incidence of the major stigmata per individual affected case varied from 25% to 100%, with a mean incidence of 70%.

3. *For the average case in each generation:* The calculation of similar incidences of these stigmata (75%, 79% and 67%) for average cases in the fourth to sixth generations, respectively (table 5), is of considerable interest, since it lends support to the theory that Marfan's syndrome is transmitted by a single pleiotropic abnormal gene; if Marfan's syndrome were transmitted by multiple linked genes, one would expect, due to the "crossing-over" of linked genes, a progressive decline in the incidence of the major stigmata for average cases in successive generations. Two other arguments have been advanced<sup>7, 20, 30</sup> in favor of the single gene theory: other syndromes consisting of multiple heritable abnormalities are believed to be caused by single genes, and parents with incomplete Marfan's syndrome have produced children showing the "full gamut of effects."

The data which have been collected from the S. family have permitted conclusions regarding fertility rates, life expectancy, and causes of death, a type of study which may be characterized as genealogic epidemiology. These data, if confirmed in other families, may provide clues to the pathogenetic mechanism underlying Marfan's syndrome, and may permit suggestions regarding genetic control of the disorder:

1. The fact that the average number of affected children born to each affected member of the family now dead was 1.4 indicates that, should this

\* In 1932, Weill<sup>11</sup> described eight patients with dislocated ocular lenses. His first clinical case was a 42 year old woman who was dwarfed and had small, stubby hands. In 1939, Marchesani<sup>35</sup> reported three siblings and one unrelated patient, each with brachymorphism and dislocated lenses, and contrasted their deformities with those of patients with Marfan's syndrome. Patients illustrating the features of the Weill-Marchesani syndrome have been reported from the United States by Meyer and Holstein,<sup>36</sup> McKusick,<sup>7</sup> Kloepfer and Rosenthal<sup>37</sup> and Zabriskie and Reisman.<sup>38</sup> To the author's knowledge, no such cases have been reported from Canada, and no families have been described in which Marfan's syndrome and the Weill-Marchesani syndrome have coexisted.

TABLE 5  
Stigmata in Affected Members of Generations IV, V and VI  
Examined by Physicians or Optometrists

Code	Lens Dislocations	Dolicho- cephaly	Gracile Limbs	Clinical Evidence of Aortic Disease	Incidence in Per cent Expressed per:	
					Individual	Generation
IV 7	+	+	+	0	75	75 Mean age = 60
IV 15	+	+	+	0	75	
IV 17	+	+	+	0	75	
V 8	?	+	0	?	50	79 Mean age = 34
V 15	+	+	+	+	100	
V 16	+	+	+	+(probable)	100	
V 17	+	+	+	0	75	
V 18	0	+	+	0	50	
V 24	+	+	+	?	100	
V 27	+	+	+	0	75	
VI 3	+	+	+	?	100	67 Mean age = 22
VI 5	+	?	0	?	50	
VI 6	+	+	+	0	75	
VI 8	+	+	0	0	50	
VI 9	+	+	+	0	75	
VI 11	+	+	0	0	50	

In this table, the stigmata known to be present are marked +, those known to be absent are marked 0, and those about whose presence or absence precise knowledge was lacking are marked ?. Throughout this paper, incidence is always expressed with reference to the number of cases in which the presence or absence of the trait is unequivocally recorded.

rate of multiplication continue, an increasing number (in a geometric progression) of affected individuals may be expected with the passage of time. Lutman and Neel<sup>20</sup> concluded from their study of the E. family that "in view of the threat to survival and reproduction imposed by Marfan's disease, it is felt that the syndrome would quickly disappear through natural selection unless there was a relatively high mutation rate from normal to the gene responsible for this syndrome." This conclusion does not seem to be supported by their own data; there were six affected members in generation II of the E. family, and 10 affected members in generation III.

2. The differences between the fertility rates of the affected males and affected females in the S. family is striking, the seven affected males now dead having had three children, and the 10 affected females now dead having had 47 children (table 3). One factor in the lower fertility rate of the affected males is undoubtedly the fact that their lifespan is shorter than that

of affected females. It seems unlikely, however, that this is the sole explanation.

3. The difference between the capacities of the affected male and the affected female members of the S. family to transmit the abnormal gene is equally remarkable, each affected male now dead having had (on the average) 0.1 affected child, while each affected female now dead had (on the average) 2.3 affected children. This difference seems entirely related to the difference in fertility rates, since approximately 50% of the children of both male and female affected members were affected. Prohibition of child-bearing by affected females would, if this difference in capacities to transmit the abnormal gene continues, result, in this family, in a rapid reduction in the number of affected members.

4. The fact that the average lifespan of the affected members of this family is shorter than that of average individuals justifies consideration of Marfan's syndrome as an "abiotrophy," i.e., a condition in which the tissues are capable of function for only a limited time because of innate weakness. Just as the average male has a shorter lifespan than the average female, so, in this family, a male with Marfan's syndrome has, on the average, a shorter lifespan than does an affected female (table 4).

5. In the absence of postmortem examinations, the data which have been collected regarding the causes of death (table 4) may be inaccurate. Most of the deaths occurred in rural areas, where the incidence of aortic disease may have been underestimated by country practitioners. That at least three deaths were attributed to aortic disease is a reflection of the ominous prognosis associated with aortic involvement in Marfan's syndrome.

The report by Whittaker and Sheehan<sup>40</sup> indicates that a consequence of aortic medionecrosis, namely, aortic dissection, may be the only evidence of Marfan's syndrome in certain patients from families transmitting Marfan's syndrome. Despite this interesting observation, it should be remembered that aortic cystic medial necrosis is a nonspecific histologic abnormality influenced by age and hemodynamic factors as well as by abnormal genes.<sup>41</sup>

The author has been impressed by the number of reported patients with Marfan's syndrome for whom French or German ancestry has been claimed. The early recognition of this syndrome by French and German clinicians undoubtedly accounts for the imposing number of French and German patients with Marfan's syndrome reported in the early part of this century. This explanation fails, however, to account for those cases with French or German parentage currently being reported from other countries—for example, the patient of French parentage described in an Australian journal by Lambie et al.;<sup>42</sup> the large family of German ancestry described by Lutman and Neel<sup>20</sup> in the United States, and the S. family of German ancestry reported from Canada. This observation has led the author to speculate regarding a possible common origin of many patients with Marfan's syndrome in a single family living near the French-German border in the eighteenth century. That such a possibility deserves consideration is illustrated by the recent report<sup>43</sup> from South Africa of several hundred patients with porphyria, all believed to have stemmed from a single individual who

married in 1688, and also by pedigrees of choreic kinships, some with as many as 1,000 affected individuals in 12 generations over a period of 350 years.<sup>44</sup>

At the present time, the treatment of the patient with Marfan's syndrome is symptomatic. The ophthalmic surgeon may carry out operative treatment of the lens dislocations or retinal detachments with some measure of success. The thoracic surgeon<sup>34</sup> may advise correction of the chest deformities; in selected cases, aortic aneurysms may be resected<sup>7</sup> or Hufnagel valves inserted.<sup>45, 46</sup> The internist may lend assistance in the treatment of heart failure, in the control of pain, and in advising restriction of childbearing. Such therapeutic measures have been discussed by others. In contrast, the importance of psychologic factors as a source of difficulty in the care of the patient with Marfan's syndrome has received scant attention in the medical literature. In a family such as has been described, it becomes common knowledge that a minor blow to the head may precipitate a retinal detachment, and that a trivial discomfort in the chest may herald the development of an aortic aneurysm. The anxieties which this knowledge engenders in the affected members of the family are compounded by the physician's inability to forestall these threats to vision or to life. Accordingly, when an affected individual develops symptoms, an already difficult therapeutic problem may be complicated by a prefabricated superstructure of realistic fears.

On the other hand, these two factors—namely, the poor results which attend medical treatment, and the constant concern regarding visual loss or sudden death—together with the heartfelt desire of these individuals not to wish the curse of Marfan's syndrome on their children, prompted most affected members of the S. family to coöperate willingly in the author's attempts to collect the data which have been presented, and to express repeatedly their gratitude for his interest in their problem.

#### CONCLUSION

Although this study has been based upon approximately one tenth of all reported cases of Marfan's syndrome (accepting McKusick's<sup>7</sup> estimate of 350 reported cases), this number of cases is too small to permit firm conclusions. Also, it would be unwise to generalize from a study of a single family to all families in which Marfan's syndrome occurs. The author believes that the principal value of the present study has been the recognition of the common origin in a single family of these individuals affected by Marfan's syndrome. He hopes that this study may provide a firm background for further investigation of the S. family, not only to confirm or deny the trends which have been observed in these six generations, but also to detect other and perhaps more important trends in succeeding generations.

A quotation from a recent oration by White<sup>47</sup> forms a fitting conclusion: "In closing may I express my confidence that in some oration in the more or less distant future the fatalism concerning the familial inheritance

of disease will be dispelled, even before the days of eugenics if such an age ever arrives, through the application of preventive measures in time to save the younger members of families who are susceptible to serious diseases such as are represented by those of the heart and blood vessels."

#### SUMMARY

At least 33 members (17 of whom are now dead) in six generations of the S. family have displayed features characteristic of Marfan's syndrome (31 cases) or suggestive of the Weill-Marchesani syndrome (two cases). If these latter two cases are accepted as examples of the Weill-Marchesani syndrome, it would seem reasonable to assume that the morphologic differences between the Weill-Marchesani syndrome and Marfan's syndrome are of insufficient importance to justify any genetic distinction between the two syndromes. The incidences of the stigmata of Marfan's syndrome in the 17 affected members known to have been examined by physicians or optometrists were: dislocation of ocular lenses, 94% of cases; dolichocephaly, 94%; arachnodactyly, 70%; clinical evidence of aortic disease, 15%. The incidences of these stigmata did not change appreciably from one generation to the next in the medically examined affected members of the fourth, fifth and sixth generations. Affected male members now dead had a lower fertility rate (average, 0.4 child each) and a lesser capacity to transmit the abnormal gene (average, 0.1 affected child each) than did affected female members (average, 4.7 children each; average, 2.3 affected children each). The average lifespan of 16 deceased affected members was 45 years. Cardiovascular diseases caused the deaths of at least 11 of 17 affected members; aortic disease accounted for at least three of the 11 deaths attributed to cardiovascular diseases.

These observations support the conclusions that, in this family, Marfan's syndrome is transmitted by a single pleiotropic abnormal gene, expression of this gene results in an abiotrophy of the cardiovascular system, and prohibition of child-bearing by affected females would be expected to reduce the number of affected individuals in succeeding generations.

#### ACKNOWLEDGMENTS

This study was begun while the author was associated with the Lockwood Clinic in Toronto, Ontario. A number of individuals and organizations lent invaluable assistance in tracing members of the S. family: the Walkerton *Herald-Times*, Walkerton, Ontario; the Registrar-General, Provincial Government Buildings, Toronto, Ontario; the Retail Credit Company, Home Office, Atlanta, Georgia, U. S. A.; Mr. Albert Batte, Walkerton, Ontario; Mrs. Elizabeth Winter, Detroit, Michigan, U. S. A.; Mrs. F. Rowan, North Bay, Ontario; and Mr. George Schneider, Mildmay, Ontario.

#### SUMMARIO IN INTERLINGUA

Al minus 33 membros (incluse 17 mortes) in sex generationes del familia S. ha exhibite tractos (1) characteristic de syndrome de Marfan (31 casos) o (2)

suggestente syndrome de Weill-Marchesani (duo casos). Le incidentia del stigmas de syndrome de Marfan in le 17 afficite membros del familia qui esseva cognoscite-mente examine per medicos o optometros esseva: Dislocation del lentes ocular, 94%; dolichocephalia, 94%; arachnodactylia, 70%; indicios clinic de morbo aortic, 15%. Le incidentia de iste stigmas non variava appreciabilemente ab un generation al altere inter le medicamento examine afficite membros del quarte, quinte, e sexte generation. Afficite membros mascule (qui es nunc morte) habeva un plus basse fertilitate (al media, 0,4 infantes per individuo) e un plus basse capacitate de transmitter le gen anormal (al media, 0,1 afficite infantes per individuo) que le afficite membros feminin (al media, 4,7 infantes e 2,3 afficite infantes per individuo). Le longevitate medie de 16 afficite e nunc morte membros esseva 45 annos. Morbos cardiovascular causava le morte de al minus 11 de 17 afficite membros. Morbo aortic esseva responsabile pro al minus tres del 11 mortes attribuite a morbos cardiovascular.

Iste observationes supporta le conclusiones que in le familia S, syndrome de Marfan es transmittite per un pleiotropic gen anormal, que le expression de iste gen resulta in un abiotrophia del systema cardiovascular, e que le prohibition de conceptiones per afficite femininas reducerea probabilemente le numero del afficite sub-jectos in generationes successive.

#### BIBLIOGRAPHY

1. Boyd, W. C.: Genetics and the races of man: an introduction to modern physical anthropology, 1st Ed., 1950, Little, Brown and Co., Boston, p. 291.
2. Rich, Mrs. William, Powasson, Ont.: Personal communication, July 3, 1957.
3. Marfan, A. B.: Un cas de déformation congénitale des quarte membres plus prononcée aux extrémités caractérisée par l'allongement des os avec un certain degré d'amincissement, Bull. et mém. Soc. méd. d. hôp. de Paris 13: 220, 1896.
4. Achard, C.: Arachnodactyly, Bull. et mém. Soc. méd. d. hôp. de Paris 19: 834, 1902, cited by Rados.<sup>5</sup>
5. Rados, A.: Marfan's syndrome, Arch. Ophth. 27: 477, 1942.
6. Boerger, F.: Ueber zwei Fälle von Arachnodactyli, Ztschr. f. Kinderh. 12: 161, 1914, and Monatsschr. Kinderh. 13: 335, 1914, cited by McKusick.<sup>7</sup>
7. McKusick, V. A.: Heritable disorders of connective tissue, Chapter III, The Marfan syndrome. Pp. 36-85. C. V. Mosby Co., St. Louis, 1st Ed. pp. 224, 1956.
8. Weve, H.: Ueber Arachnodactylie (Dystrophia mesodermalis congenita, Typus Marfanis), Arch. f. Augenh. 104: 1, 1931.
9. Baer, R. W., Taussig, H. B., and Oppenheimer, E. H.: Congenital aneurysmal dilatation of the aorta associated with arachnodactyly, Bull. Johns Hopkins Hosp. 72: 309, 1943.
10. Etter, L. E., and Glover, L. P.: Arachnodactyly complicated by dislocated lens and death from dissecting aneurysm of the aorta, J. A. M. A. 123: 88, 1943.
11. Weill, G.: Ectopie du cristallin et malformations générales, Ann. d'ocul. 169: 21, 1932.
12. Williams, E.: Rare cases, with practical remarks, Tr. Am. Ophth. Soc. 2: 291, 1876.
13. Méry, H., and Babonneix, L.: Un cas de déformation congénitale des quatre membres: hyperchondroplasia, Bull. et mém. Soc. méd. d. hôp. de Paris 19: 671, 1902, cited by Rados.<sup>5</sup>
14. Ponseti, I. V., and Shepard, R. S.: Lesions of the skeleton and of other mesodermal tissues in rats fed sweet-pea *Lathyrus odoratus* seeds, J. Bone and Joint Surg. 36A: 1031, 1954.
15. Patterson, W. J.: Case of arachnodactyly, Canad. M. A. J. 28: 652, 1933.
16. Gibson, R.: The incidence of arachnodactyly in an institutional population, Canad. M. A. J. 75: 501, 1956.

17. Gibson, R., Portage la Prairie, Manitoba: Personal communication, Jan. 17, 1958.
18. Fay, J. E., Horlich, L., Merriman, J. E., and Nanson, E. M.: A case of Marfan's syndrome with an aneurysm at the ascending aorta with physiologic, operative and post-mortem studies, *Canad. M. A. J.* **78**: 862, 1958.
19. Baker, C. B., Wilson, J. K., and Woods, J. S.: Marfan's syndrome—a successful aortic homograft for a dissecting aneurysm of the thoracic aorta, *Canad. J. Surg.* **1**: 371, 1958.
20. Lutman, F. C., and Neel, J. V.: Incidence of arachnodactyly, ectopia lentis and other congenital anomalies (Marfan's syndrome) in the E. family, *Arch. Ophth.* **41**: 276, 1949.
21. Wilson, R.: Marfan's syndrome: description of a family, *Am. J. Med.* **23**: 434, 1957.
22. Bowers, D.: Marfan's syndrome and the Weill-Marchesani syndrome in the S. family (abstract), *Circulation* **18**: 696, 1958; also in *Festschrift* volume for Dr. P. S. Hench, Oct. 1, 1958.
23. Robertson, N.: The history of the county of Bruce and of the minor municipalities therein, Province of Ontario, Canada, 1906, William Briggs, Toronto, p. 560.
24. Abstract of clinical record, Toronto General Hospital, Toronto, Ontario.
25. Abstract of clinical record, University of Alberta Hospital, Edmonton, Alta.
26. Cohen, S. J., North Bay, Ontario: Personal communication, Jan. 20, 1958.
27. Kellett, Miss V., Ontario School for the Blind, Brantford, Ontario: Personal communication, Aug. 6, 1957.
28. Richardson, Dr. O. B., Toronto, Ont.: Personal communication, July 16, 1957.
29. Batte, Albert, Walkerton, Ontario: Personal communication, Oct. 14, 1957.
30. Steinberg, I., Mangiardi, J. L., and Noble, W. J.: Aneurysmal dilatation of the aortic sinuses in Marfan's syndrome: angiocardiographic and cardiac catheterization studies in identical twins, *Circulation* **16**: 368, 1957.
31. Abstract of necropsy report, Toronto General Hospital, Toronto, Ontario.
32. Lester, C. W.: The etiology and pathogenesis of funnel chest, pigeon breast and related deformities of the anterior chest wall, *J. Thoracic Surg.* **34**: 1, 1957.
33. Kilgore, G. L.: Arachnodactyly (Marfan's syndrome) and its eye complications, *Tr. Pacific Coast Oto-Ophth. Soc.* **24**: 223, 1939.
34. McKusick, V. A.: The cardiovascular aspects of Marfan's syndrome: a heritable disorder of connective tissue, *Circulation* **11**: 321, 1955.
35. Marchesani, O.: Brachydactyly and congenital spherophakia as a systemic disease, *Klin. Monatsbl. f. Augenheut.* **103**: 392, 1939, cited by Meyer and Holstein,<sup>8a</sup> and in Jubilee volume for Prof. Vogt, Part II, p. 32, 1939, B. Schwabe, Basle, cited by McKusick.<sup>7</sup>
36. Meyer, S. J., and Holstein, T.: Spherophakia with glaucoma and brachydactyly, *Am. J. Ophth.* **24**: 247, 1941.
37. Kloepper, H. W., and Rosenthal, J. W.: Possible genetic carriers in the spherophakia-brachymorphia syndrome, *Am. J. Human Genet.* **7**: 398, 1955.
38. Zabriskie, J., and Reisman, M.: Marchesani syndrome, *J. Pediat.* **52**: 158, 1958.
39. Sinclair, R. J. G.: The Marfan syndrome, *Bull. Rheumat. Dis.* **8**: 153, 1958.
40. Whittaker, S. R. F., and Sheehan, J. D.: Dissecting aortic aneurysm in Marfan's syndrome, *Lancet* **2**: 791, 1954.
41. Heath, D., Edwards, J. E., and Smith, L. A.: The rheologic significance of medial necrosis and dissecting aneurysm of the ascending aorta in association with calcific aortic stenosis, *Proc. Staff Meet., Mayo Clin.* **33**: 228, 1958.
42. Lambie, C. G., Shellshear, K. E., and Shellshear, J. L.: Arachnodactyly or Marfan's syndrome, *M. J. Australia* **1**: 213, 1950.
43. Dean, G., and Barnes, H. D.: Porphyria: a South African screening experiment, *Brit. M. J.* **1**: 298, 1958.

44. Pearson, J. S., Peterson, M. C., Lazarte, J. A., Blodgett, H. E., and Kley, I. B.: An educational approach to the social problem of Huntington's chorea, *Proc. Staff Meet., Mayo Clin.* **30**: 349, 1955.
45. Dimond, E. G., Larsen, W. E., Johnson, W. B., and Kittle, C. F.: Post-traumatic aortic insufficiency occurring in Marfan's syndrome with attempted repair with a plastic valve, *New England J. Med.* **256**: 8, 1957.
46. Case records of the Massachusetts General Hospital: case No. 43011, *New England J. Med.* **256**: 30, 1957.
47. White, P. D.: Annual discourse: genes, the heart and destiny, *New England J. Med.* **256**: 965, 1957.

## CASE REPORTS

### THE DIAGNOSIS OF ACUTE VIRAL HEPATITIS SIMULATING AN ABDOMINAL EMERGENCY: A CASE REPORT \*

By ELLIS L. ROLETT, M.D.,† and MARVIN H. SLEISINGER, M.D.,  
*New York, N. Y.*

ALTHOUGH abdominal pain is common in the preicteric phase of acute viral hepatitis, it is rarely of sufficient intensity to simulate an acute surgical condition; occasionally, however, there is not only severe distress but also marked upper abdominal tenderness, direct and rebound. Because of the dangers in laparotomy in individuals with liver disease, awareness that hepatitis may simulate an abdominal disorder which requires surgery is important. Correct early diagnosis is imperative, and may be facilitated by measurement of serum glutamic oxaloacetic transaminase and the clinical effect of corticotropin (ACTH). Our recent experience with such a patient is reported.

#### CASE REPORT

The patient, a 28 year old registered nurse, was admitted to The New York Hospital complaining of upper abdominal pain of one day's duration. She had been in excellent health until three days prior to admission, when she awoke with chills, fever and anorexia. Two days before hospitalization she became nauseated, vomited repeatedly, and had a temperature of 105° F. In the afternoon of the day before admission she noted a "sore spot" localized to the midepigastrium, which became increasingly severe and prevented sleep the night before entry. It remained localized to the same small area in the midepigastrium and was cramping, but assumed an intensely sharp quality with local pressure, coughing or jarring. It did not radiate, nor was it referred to the shoulders or back. The pain was further aggravated by lying in the supine position, and was relieved, sometimes completely, by leaning forward in a sitting position or by lying prone. The patient had not noted dark urine, light stools, jaundice or pruritus. There was no history of food intolerance, blood transfusion, or exposure to a known hepatotoxic agent. The patient used alcohol sparingly, and used no drugs except aspirin.

The past history was negative.

Physical examination revealed an anicteric young woman with severe abdominal pain who was acutely ill and dehydrated. The temperature was 38.6° C. Positive findings included small cervical and axillary lymph nodes. Examination of the abdomen demonstrated exquisite tenderness, direct and rebound, localized to a small area high in the epigastrium. The upper portions of the rectus muscles were in spasm. The tenderness extended into the right upper quadrant, where the liver was

\* Received for publication July 23, 1958.

From the Department of Medicine, The New York Hospital-Cornell Medical Center, New York, N. Y.

† Present address: Captain, 7520th USAF Hospital, South Ruislip, England.

Requests for reprints should be addressed to Marvin H. Sleisenger, M.D., Associate Professor, Department of Medicine, The New York Hospital-Cornell Medical Center, 525 East Sixty-eighth Street, New York 21, N. Y.

enlarged by percussion below the right costal margin but could not be palpated because of spasm. The spleen was not palpable. Severe sharp pain was referred to the same area in the epigastrium with coughing and with the lightest percussion of any part of the abdomen. The bowel sounds were hypoactive.

Routine laboratory studies showed a dark yellow urine with 1 plus albumin, 2 plus bile, urobilinogen of 1:64, and no porphobilinogen by the Watson-Schwartz method. The white blood count was 4,000/cu. mm., with the following differential count per 100 cells: 4 mature polymorphonuclears, 32 band polymorphonuclears, 1 metamyelocyte, 42 lymphocytes, 18 monocytes, 2 eosinophils and 1 basophil. Approximately half of the lymphocytes were atypical, with cytoplasmic vacuoles, deeply basophilic cytoplasm, azurophilic cytoplasmic granules, or nucleoli (figure 1). The hematocrit was 43%. The Mazzini test was negative. The blood urea nitrogen

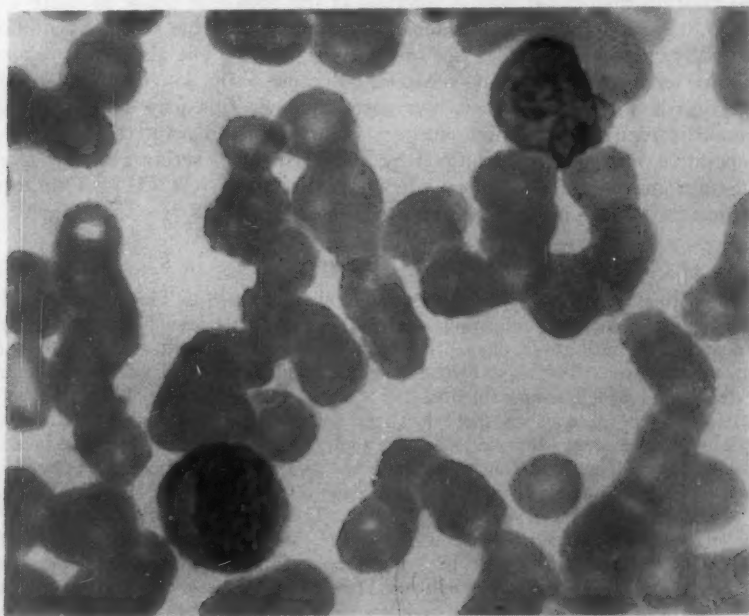


FIG. 1. Peripheral blood smear demonstrating two "viruscytes."

was 9 mg.%; total bilirubin, 1.6 mg. per 100 ml., with 1.3 mg. direct and 0.3 indirect (normal: total, 0.2-1.0 mg. per 100 ml.); alkaline phosphatase, 5.4 Bodansky units; thymol turbidity, 6 units (normal, 0 to 4 units); amylase, 61 units (normal, 40 to 110 units); lipase, 0.9 ml. of N/100 NaOH per cubic centimeter of serum (normal, 0.2 to 2.0 c.c.). On the second hospital day the serum glutamic oxaloacetic transaminase was 2,668 units per milliliter per minute as determined by the spectrophotometric assay method (normal, 5 to 40 units).<sup>1</sup> The heterophil agglutination was 1:56, the amebic complement fixation test was negative, and a blood culture was sterile. X-rays of the chest and abdomen were normal except for slight splenic enlargement.

The day following admission the skin began to appear slightly icteric. Forty-five hours after admission, in a setting of continuing exquisite epigastric pain, fever,

anorexia, nausea, vomiting and elevated serum transaminase, the patient was given a single injection of ACTH gel, 80 units intramuscularly (figure 2). Her temperature promptly fell, and within 12 hours of the injection she was hungry and able to eat, being completely free of nausea and vomiting. The transaminase had fallen to 1,480 units at that time. Twenty-four hours after the administration of ACTH the

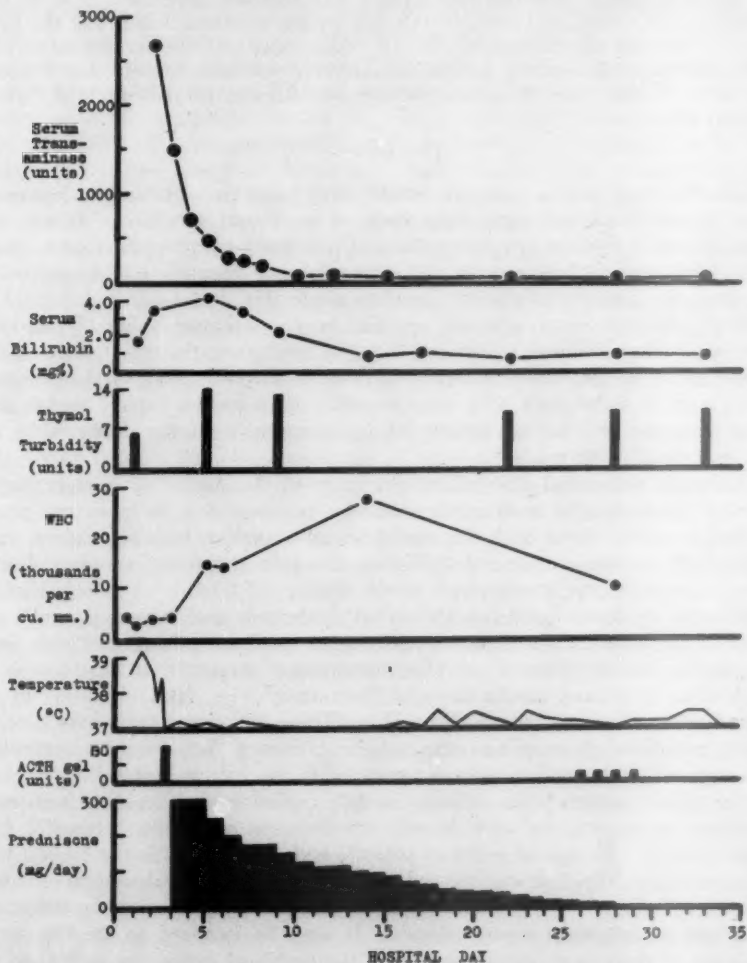


FIG. 2. Clinical course of patient.

abdominal pain and muscle spasm had almost disappeared and it was possible to palpate the liver edge, which extended from 3 cm. below the right costal margin across into the epigastrium 11 cm. below the xiphoid process. However, marked hepatic tenderness persisted for 10 days. Following this injection of ACTH the patient was placed on high oral doses of prednisone, starting with a total daily dose

of 300 mg., which was gradually tapered off over a 25-day period (figure 2). The transaminase, which fell off sharply after the beginning of steroid therapy, gradually returned to within normal limits by the twenty-first day of treatment. The patient continued in a state of well-being for the four and one-half weeks of her hospital stay after the institution of corticosteroid therapy. She was able to maintain a daily food intake of nearly 3,000 calories. There was transient glycosuria only on the higher doses of prednisone; she felt well, her weight remained stable, and the liver gradually returned toward normal size. A repeat heterophil titer at discharge was 1:56. Two months later the patient was working full-time, without any residual symptoms. At that time her serum bilirubin was 0.3 mg. per 100 ml., and thymol turbidity was 3 units.

#### COMMENTS

The diagnosis in this case was acute viral hepatitis. Strikingly, however, the early symptoms and signs were those of a surgical condition. It was the leukopenia with relative lymphocytosis and abnormal lymphocytic forms which discouraged surgical intervention, but although viral hepatitis was suspected at this time, the absence of clinical jaundice made this diagnosis doubtful. The markedly elevated serum glutamic oxaloacetic transaminase value obtained 30 hours after admission was therefore crucial in confirming the true nature of her illness; and in the absence of a history of blood transfusion, parenteral injections, or exposure to individuals with viral hepatitis or to known hepatic toxins, and in the presence of a normal heterophil agglutination titer, the diagnosis of infectious hepatitis was made.

Although abdominal discomfort, generally in the nature of a right upper or lower quadrant ache or dragging sensation, is common in the preicteric phase of viral hepatitis, along with the symptoms of anorexia, malaise, nausea, constipation or diarrhea, fever and chilliness, this pain frequently subsides shortly after the onset of the icteric phase of the disease.<sup>2, 3, 4, 5, 6, 7, 8, 9</sup> On palpation, right upper or lower quadrant abdominal tenderness and spasm generally accompany the discomfort. Intense right upper quadrant aching and pain were conspicuous among cases of so-called "malignant" hepatitis in Scandinavia in the 1940's,<sup>10, 11, 12</sup> and among cases of "fulminant" (i.e., fatal) hepatitis in the United States Army in World War II.<sup>13</sup> These symptoms and signs have so closely resembled those of an acute surgical abdomen that surgical intervention for suspected acute cholecystitis or appendicitis has been reported.<sup>6, 7, 9, 11, 12</sup>

An added problem is the difficulty in differentiating viral hepatitis from early infectious mononucleosis with hepatic involvement when the heterophil titer is still normal. In several series of patients with viral hepatitis the highest titer obtained was 1:56, which was reduced to 1:7, or negative, by adsorption on boiled guinea pig kidney.<sup>14, 15</sup> In addition, abdominal pain may be an early and major complaint in infectious mononucleosis. It may be localized to the left upper quadrant, if there is a splenic tear, or to the umbilical region, as well as to the right upper and lower quadrants.<sup>16-19</sup> Some of these patients also have come to operation for suspected acute appendicitis.

In our patient the initial serum transaminase value was 2,668 units. The diagnostic significance of serum transaminase elevation in acute hepatitis is well known, the enzyme being elevated in the prodromal phase before jaundice occurs, and frequently before abnormalities appear in the other liver function

tests.<sup>20</sup> However, it was the leukopenia and relative lymphocytosis which initially suggested the diagnosis of hepatitis in this case.

Since the first use of corticotropin in infectious hepatitis<sup>21</sup> there have been numerous reports on the use of ACTH, cortisone and prednisone, with varying conclusions as to the efficacy of these agents.<sup>22, 23, 24</sup> The value of these agents in this disease lies in the improvement of appetite, defervescence, decrease in jaundice and, important to the present discussion, decrease in abdominal discomfort. Of further significance are the reported cases of viral hepatitis where a rapidly worsening course, or even a state of hepatic coma, was reversed coincident with the administration of ACTH or cortisone.<sup>25, 26</sup> However, unless the possibility of a surgical condition of the abdomen is excluded with some degree of certainty, one would hesitate to employ corticotropin or one of the corticosteroids, since these agents may mask all signs of peritonitis.<sup>27</sup> Because of the marked nausea, persistent vomiting, anorexia, and severity of the abdominal pain, corticotropin therapy followed by prednisone was instituted. The ensuing clinical improvement was dramatic, and coincided with the return of the deranged blood chemistry values toward normal (figure 2). It is probable that this abrupt change in clinical course and level of serum transaminase was closely related to steroid therapy and, although not pathognomonic, helped support the diagnosis of viral hepatitis. It is possible that a continuing downhill course was averted.

The full explanation of the origin of abdominal pain in hepatitis is not apparent. Clearly the symptoms seem to be those of peritoneal irritation (one would assume the visceral peritoneum of the liver), but whether mere stretching of the liver capsule with enlargement of the liver is sufficient to produce pain of this nature, or whether actual inflammatory changes of the capsule are necessary to produce signs of peritoneal irritation, is not evident. It is possible that inflammation of the hepatic parenchyma itself plays a part, since right upper quadrant pain is found in instances of rapid necrosis and shrinkage of the liver. Abdominal pain in infectious mononucleosis has been attributed to enlarged retroperitoneal and mesenteric lymph nodes,<sup>16</sup> and this may be a factor in viral hepatitis. An interesting feature of the case under discussion is the striking pain relief that the patient noted when leaning forward in a sitting position or lying face down. Relief of abdominal pain by these maneuvers occurs in eroding retroperitoneal tumors and pancreatitis, and recently has been reported in intermittent ischemia of the mesenteric arterial circulation.<sup>28</sup> Of interest is the fact that a similar mechanism of pain relief has been noted in cases of infectious mononucleosis where abdominal pain has been prominent.<sup>17, 19</sup> If involvement of the retroperitoneal lymph nodes contributes to the epigastric pain, the mechanism of relief of pain by lying prone or sitting forward may be that of reduction of pressure on the celiac and splanchnic plexuses by gravitational shift of the involved nodes.<sup>28</sup>

#### SUMMARY

A case is described of infectious hepatitis which initially presented the clinical picture of an acute surgical condition of the abdomen. A markedly elevated serum glutamic oxaloacetic transaminase value helped to establish the diagnosis in the absence of clinical jaundice. The prompt clinical and laboratory response

to ACTH and prednisone therapy lent confirmatory evidence. Possible explanations for the abdominal pain of viral hepatitis are discussed.

#### SUMMARY IN INTERLINGUA

Un infirmiera de 28 annos de etate, con bon sanitate durante su integre vita passate, experienciava subitementamente algore e febre (105 F) associate con nausea e vomito durante duo dies, sequite per gradualmente crescente dolores in le meso-epigastrio. Istos esseva crampose sed deveniva acute con tusse, motion, o pressura. Illos persisteva durante 18 horas ante le admission del patiente al Hospital New York. Il habeva in iste caso nulle historia de transfusion de sanguine o de injectiones anterior. Le examine physic revelava un anicteric juvene femina con un temperatura de 38,5 C e sensibilitate extreme sub pression e in relaxation de pression in le epigastrio alte, con rigiditate muscular in iste area. Le sensibilitate se notava etiam in le quadrante dextero-superior. Le hepate se monstrava allargate in percussione.

Le datos laboratorial pro le prime die al hospital includeva le sequentes: Hematocrite, 43%; numeration leucocytic, 4.000/mm<sup>3</sup>, con 42% lymphocytos e 13% monocytos; un medietate del lymphocytos esseva atypic. Le contento de bile in le urina esseva 2 plus e le urobilinogeno 1:64. Le amylase esseva 61 unitates e le bilirubina total 1,6 mg pro 100 ml (directe 1,3 e indirecte 0,3). Le secunde die, le seral transaminase glutamic-oxaloacetic esseva 2.668 unitates per millilitro per minuta. Le agglutination heterophile esseva 1:56. Un roentgenogramma plan del abdomine revelava un leve allargamento del splen.

Verso le fin del secunde die al hospital, con ictero apparente, le combination del aspectos clinic de continue grados sever de dolor epigastric, de febre, de anorexia, de nausea, e de vomito con un persistente elevation de transaminase justificava un essayo con therapia steroide. Post un injection intramuscular de 80 unitates de gel de ACTH, il occurreva un prompte defervescentia, le restitution del appetito, e le disparition de nausea e vomito, accompagnate de un pronunciate reduction del transaminase. Vinti-quatro horas plus trade, le dolores abdominal, le sensibilitate, e le spasmos subsideva sufficientemente pro permettre le palpation de un allargate hepate que esseva sensibile sub pression. A iste tempore, prednisona oral in un dosage de 300 mg per die esseva prescribite. In le curso de 25 dies iste dosage esseva reduce gradualmente. Durante iste periodo, le sensibilitate del hepate e le ictero dispareva gradualmente. Le patiente mangiava plus que 3.000 calorias per die. Quatro septimanas post le admission illa esseva dimittite.

Le patiente habeva omne le signos physic de un acute condition intra-abdominal requirente un intervention chirurgic e probabilemente locate in le vias biliari. Tamen, le leucopenia, le lymphocytos anormal, le elevate nivello seral de transaminase, e le prompte responsa clinic al administration de ACTH supportava le diagnose de hepatitis viral in despecto del admission de jalnessa al tempore del hospitalisation. Es discutate le mecanismos possibile de tal dolores causate per le inflammation del hepate.

#### BIBLIOGRAPHY

1. Karmen, A., Wroblewski, F., and LaDue, J. S.: Transaminase activity in human blood, *J. Clin. Investigation* **34**: 126-133, 1955.
2. Havens, W. P., Jr.: Infectious hepatitis, *Medicine* **27**: 279-326, 1948.
3. Bates, R.: Non-spirochaetal infectious jaundice, *Brit. M. J.* **1**: 521-524, 1936.
4. Findlay, G. M., Martin, N. H., and Mitchell, J. B.: Hepatitis after yellow fever inoculation, relation to infectious hepatitis, *Lancet* **2**: 301-307, 1944.
5. Barker, M. H., Capps, R. B., and Allen, F. W.: Acute infectious hepatitis in the Mediterranean Theater, *J. A. M. A.* **128**: 997-1003, 1945.

6. Bank, J., and Cheskin, L. J.: Hepatitis as observed in an Army general hospital, *Gastroenterology* **6**: 357, 1946.
7. Hardy, H. L., and Feemster, R.: Infectious hepatitis in Massachusetts, with a review of present knowledge of the disease, *New England J. Med.* **235**: 147, 1946.
8. Neeffe, J. R.: Viral hepatitis, *Am. J. Med.* **16**: 710-728, 1954.
9. Lewis, H. P.: Pain in acute and chronic diseases of the liver, *Ann. Int. Med.* **35**: 878-888, 1951.
10. Jersild, M.: Infectious hepatitis with subacute atrophy of the liver, *New England J. Med.* **237**: 8, 1947.
11. Alsted, G.: Studies on malignant hepatitis, *Am. J. M. Sc.* **213**: 257-267, 1947.
12. Salvesen, H. A., and Lodoen, O.: Clinical studies on malignant hepatitis, *Acta med. Scandinav.* **137**: 305-321, 1950.
13. Lucke, B., and Mallory, T.: The fulminant form of epidemic hepatitis, *Am. J. Path.* **22**: 867, 1946.
14. Havens, W. P., Jr., Gambescia, J. M., and Knowlton, M.: Results of heterophile antibody agglutination and Kahn tests in patients with viral hepatitis, *Proc. Soc. Exper. Biol. and Med.* **67**: 437-440, 1948.
15. Berk, J. E., Shay, H., Ritter, J. A., and Siplet, H.: Infectious mononucleosis and infectious hepatitis: studies bearing on certain resemblances and differences, *Gastroenterology* **11**: 658-671, 1948.
16. Bernstein, A.: Infectious mononucleosis, *Medicine* **19**: 85-159, 1940.
17. Perisho, G. M., and Sargent, D. U.: Acute infectious mononucleosis simulating acute abdominal emergency: report of four cases occurring aboard ship, *U. S. Nav. M. Bull.* **45**: 215-220, 1945.
18. Wechsler, H. F., Rosenblum, A. H., and Sills, C. T.: Infectious mononucleosis: report of an epidemic in an Army post. Part I, *Ann. Int. Med.* **25**: 113-133, 1946.
19. Wormer, D. C., Martin, W. J., and Wollaeger, E. E.: Infectious mononucleosis with jaundice and abdominal pain as presenting complaints: report of a case, *Ann. Int. Med.* **45**: 718-724, 1956.
20. Wroblewski, F., Jervis, G., and LaDue, J. S.: The diagnostic, prognostic and epidemiologic significance of serum glutamic oxaloacetic transaminase (SGO-T) alterations in acute hepatitis, *Ann. Int. Med.* **45**: 782-800, 1956.
21. Colbert, J. W., Jr., Holland, J. F., Heisslar, I., and Knowlton, M.: The use of ACTH in acute viral hepatitis, *New England J. Med.* **245**: 172-176, 1951.
22. Evans, A. S., Sprinz, H., and Nelson, R. S.: Adrenal hormone therapy in viral hepatitis. I. The effect of ACTH in the acute disease, *Ann. Int. Med.* **38**: 1115-1133, 1953.
23. Sborov, V. M., Giges, B., Plough, I. C., and Mandel, W.: ACTH therapy in acute viral hepatitis, *J. Lab. and Clin. Med.* **43**: 48-57, 1954.
24. Johnson, E. C., and Bennett, H. D.: ACTH in the treatment of infectious hepatitis, *Gastroenterology* **28**: 265-273, 1955.
25. Rifkin, H., Marks, L. J., Hammerman, D. J., Blumenthal, M. J., Weise, A., and Weingarten, B.: Use of corticotropin and cortisone in acute homologous serum hepatitis, *Arch. Int. Med.* **89**: 32-40, 1952.
26. Ducci, H., and Katz, R.: Cortisone, ACTH and antibiotics in fulminant hepatitis, *Gastroenterology* **21**: 357-374, 1952.
27. Boling, L., Newkirk, J., Baxter, P., Partridge, J., Margen, S., and Kinsell, L. W.: The use of ACTH in the management of generalized peritonitis. A preliminary report, *J. Clin. Endocrinol. and Metabolism* **12**: 184-190, 1952.
28. Sedlacek, R. A., and Bean, W. B.: Abdominal "angina": the syndrome of intermittent ischemia of mesenteric arteries, *Ann. Int. Med.* **46**: 148-152, 1957.

## FAMILIAL CONGENITAL METHEMOGLOBINEMIA: REPORT OF A CASE AND FAMILY STUDY \*

By H. E. DEPREE, M.D., F.A.C.P., *Kalamazoo, Michigan*, and M. J. HICKMAN, M.D., *Madison, Wisconsin*

FAMILIAL congenital methemoglobinemia is an unusual disease state. A total of somewhat over 100 cases has been reported<sup>2</sup> in the literature, and only 13 families where multiple members have the disease (familial form).

It is our impression that clinicians in the private practice of medicine often share a feeling that the unusual diseases appear, mostly if not entirely, in the large institutions or centers of medicine. This feeling is gained principally from the reporting of diseases and their incidence in the literature, which must of necessity come out of adequately large series of cases, specialized diagnostic facilities, and other situations possible only in medical centers.

The experience we are reporting, however, proves that congenital familial methemoglobinemia, at least, may appear in a private practice in a relatively small community, and therefore assumes some importance in the differential diagnosis of clinical problems presenting these features. Our experience with the patient reported below reemphasizes what others (i.e., Gasul et al.) have reported, in that a differentiation from congenital cyanotic heart disease is the most frequent presenting problem. In this case a rather dramatic episode led our attention to a consideration of the true diagnosis. The recognition of the condition in the index case enabled us to uncover three other cases in the same family.

### CASE REPORT

A 31 year old married female was admitted to Bronson Methodist Hospital, Kalamazoo, Michigan, on February 1, 1958, after having had recurrent crampy abdominal pain for several days, during which time she had reportedly passed several tarry stools. The night following admission she suddenly developed syncope following an enema; she became pulseless, and respirations ceased. After the administration of adrenalin, heart beats and respiration resumed. However, because of hypotensive levels of blood pressure, Levophed was administered by continuous intravenous drip; oxygen was given by tent.

Past history revealed that the patient had been "blue" all her life, had had definite exertional dyspnea as a child, and at the age of 20 had been told that she had an enlarged heart. She had had episodes of syncope all her life at relatively infrequent intervals. Approximately one year before admission she had been hospitalized because of syncope. A muscle biopsy of the left deltoid done at that time was reportedly negative. She was told that there was disease of the pelvic organs, and was apparently treated with irradiation to the pelvis.

On examination the patient was 5'3½" tall and weighed 131 pounds. There was intense cyanosis of the lips, mucous membranes, nail-beds and toes. There was no clubbing of the fingers, dyspnea, fullness of the veins or ankle edema. Lungs were clear to percussion and auscultation. Blood pressure was 100/70 mm. of Hg. Apical rate was 70 beats per minute. No murmurs were heard. The pulmonary

\* Received for publication January 5, 1959.

From the Bronson Methodist Hospital, Kalamazoo, Michigan.

Requests for reprints should be addressed to H. E. DePree, M.D., 216 Bronson Medical Center, Kalamazoo, Michigan.

second sound was louder than the aortic second sound and split. The abdomen was soft and without tenderness, and the liver was not palpable. Pelvic examination with within the limits of normal as was the neurologic examination.

*Laboratory Data:* Hemoglobin, 17.7 gm.; white blood cells, 11,050, with polymorphonuclears, 79%; lymphocytes, 18%; eosinophils, 2%; mononuclears, 1%. Oxygen content of arterial blood by van Slyke analysis (right radial artery) was 14.6 vol.% and 99.4% saturated. Color index, 0.85; volume index, 0.80; saturation index, 1.06; mean corpuscular hemoglobin (MCH), 27; mean corpuscular volume (MCV), 79; mean corpuscular hemoglobin concentration (MCHC), 35%. Urinalysis showed a specific gravity of 1.023; the sediment contained 50 to 60 white cells and two to four red cells per high power field. Stool gave a negative guaiac test. Blood Kline test was negative; blood urea nitrogen, 19 mg.%; calcium, 11 mg.%.

A spinal tap was done. The opening pressure was 220 mm. water. The spinal fluid contained: lymphocytes, 2; sugar, 85 mg.%; protein, 78 mg.%; globulin, negative; chlorides, 680 mg.%; Kline test, negative; gold curve, 1111100000.

Repeat urinalysis (catheterized specimen) was negative for red cells, and cultures failed to reveal any growth. Serum bilirubin: direct, 0.12 mg., indirect, 0.48 mg., giving a total of 0.60 mg. Ascorbic acid level while the patient was on a general diet was 0.65 mg.%.

Upper gastrointestinal x-rays were negative except for a diverticulum of the third part of the duodenum; colon x-rays were negative. Fluoroscopic studies of the heart and lungs were negative. An electrocardiogram showed a rate of 71, with sinus rhythm, PR interval of 0.18, QRS of 0.08, QT of 0.40, and was entirely within normal limits. Ear lobe oximetry recorded while the patient was in the oxygen tent was 74%. Bone marrow was reported as hyperplastic marrow, but there was no evidence of any blood dyscrasia.

*Hospital Course:* Because of the episode of syncope without evidence of any bleeding, and in the face of a normal electrocardiogram, an electroencephalogram was done to rule out the possibility of a brain tumor. It was reported as "borderline abnormal, non-specific." The patient was then studied as to the possibility of congenital heart disease. The advisability of cardiac catheterization was being considered when the history of two sisters and a brother, cyanotic since birth, was obtained. These siblings, all older than our patient, are still living and apparently well. The diagnosis of congenital methemoglobinemia was then entertained. After a base line level of 25% methemoglobin (spectroscopic) in the venous blood had been obtained, the patient was started on ascorbic acid, 500 mg. intravenously, followed by 50 mg. orally four times a day. The patient's color became less cyanotic, and after two weeks of therapy the methemoglobin was reported as 15%. The patient subjectively became markedly improved, and has been able to return to work.

#### DISCUSSION

Much has already been published regarding the postulated etiologic mechanisms involved in congenital methemoglobinemia. Gibson (1948) is credited with the most generally accepted pathophysiologic explanation.<sup>3</sup> Briefly, hemoglobin containing ferrous iron is constantly being oxidized to ferric hemoglobin, even in normal blood. This process is checked by the action of a reducing system within the red cells involving coenzyme I and diaphorase I, so that the content of oxidized hemoglobin or methemoglobin never reaches more than 2%. The congenital methemoglobinemic individual, however, is said to possess deficient diaphorase I activity, and consequently the methemoglobin production reaches a higher level.<sup>1, 3, 4</sup> A level of at least 20% (or 2 to 3 gm. of the

hemoglobin in the form of methemoglobin) is said to produce clinically abnormal coloration.<sup>8</sup>

Of further interest as to the mechanism are the different modes of action of the therapeutic agents, methylene blue and ascorbic acid. As proposed by Breaky, Gibson and Harrison,<sup>3</sup> methylene blue, when present, augments reduction of methemoglobin by an alternate reducing system involving diaphorase II, whereas ascorbic acid is felt to act directly as a reducing agent on methemoglobin.<sup>3</sup>

The effect of these agents has a limited duration, and therapy must be continuous in order to sustain the reduction of the methemoglobin content of the red cells. Thus lapses or discontinuance of therapy results in a resurgence of the original levels of methemoglobinemia.<sup>1, 3, 4</sup> This response would be in contradistinction to that expected in the acquired forms of methemoglobinemia, where possible methemoglobin-producing agents have been removed, so that, with reduction of the formed methemoglobin, none further would be produced, even after discontinuance of methylene blue or ascorbic acid therapy. This response might conceivably serve as a diagnostic aid in questionable cases. Ordinarily, however, this situation would not arise because of the usually rapid recovery to normal hemoglobin content of cases with acquired forms of methemoglobinemia after simply removing the oxidizing agent.

The clinical manifestations of the condition have not been widely or completely described or commented upon, except for brief descriptions in case reports, and in reference to its distinction from other, possibly confusing diagnostic possibilities.<sup>6</sup> In the newborn infant the condition may be quite threatening, and death as a result of hypoxia apparently may result.<sup>7</sup> Most reported infants, however, have survived, and the adults described have shown surprisingly little serious morbidity or disabling symptomatology.<sup>5</sup> This may account for the lack of preoccupation in the literature with descriptions of clinical manifestations. Exertional dyspnea, fatigue and lassitude and, occasionally, syncopal episodes may be seen. Our case is of some interest in this regard because of the rather dramatic episode which involved apparent cessation of effective cardiac or respiratory activity. This was followed by a period of 48 hours of hypotension, which we believe can be accounted for by background effect of chronic hypoxia, triggered perhaps reflexly by the administration of a cleansing enema. However, the patient had actually recovered from this episode before effective treatment to correct the methemoglobinemia was instituted. This would again seem to attest to the relatively subclinical effect of this condition. As a matter of fact, one of the most striking aspects noted in observing this case was the apparent lack of any respiratory or cardiovascular distress, despite a grossly cyanotic hue and the purplish color of the arterial blood.

The hereditary aspects of congenital methemoglobinemia have been studied and reported.<sup>4, 8</sup> Some confusion in nomenclature exists, we believe, in that sporadic reported cases where no other cases have been established in the family have been termed simply "congenital" or "idiopathic" methemoglobinemia. Where at least one or more siblings with the disease have been found, the terms "familial congenital," or "familial idiopathic methemoglobinemia," or "hereditary methemoglobinemic cyanosis" have been used. One wonders if most cases would not be shown to be hereditary if an adequate search of the genealogy was made.

There exists some apparent divergence of opinion as to the mode of trans-

mission.<sup>1, 8</sup> It would seem that the gene may be transmitted as either a dominant or a recessive character. With the generous assistance of Dr. R. Greene, of Rensselaer, Indiana, and Dr. Allen, of Martin, Kentucky, we were able to obtain blood samples from and to interview most of the principal members of the family of our index case, and thus to work out a pedigree (figure 1).

All of the cases whose blood was actually sampled, and those reported by interview, are seen to belong to the same generation, whereas the preceding and succeeding generations are apparently free of the disease. Codounis' Melanarides family presented skipping of one generation and then direct transmission in a succeeding transference.<sup>8</sup> Baikie and Voltis<sup>4</sup> show a pedigree with cases in two succeeding generations and then a free generation. Codounis labels intermediary members as carriers, and the youngest generation has thus far

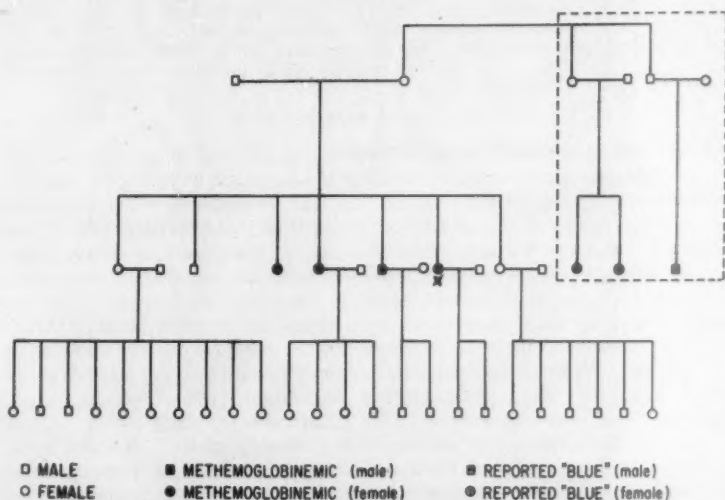


FIG. 1. Pedigree of index case (X indicates index case). Venous blood samples were obtained and analyzed spectroscopically for methemoglobin from all members of this pedigree with the exception of those enclosed by the dotted line.

apparently been skipped. This pedigree would seem to indicate transmissions as a recessive character in our family study. The percentage of methemoglobin in the siblings is listed in table 1. The relative constancy of the percentage among these siblings seems of interest, and possibly suggests a constancy of the defect for a given family.

The three affected siblings of our index case are apparently without symptomatology, as far as we have been able to determine. Pregnancy and surgical procedures have apparently been tolerated by all cases with no adverse effects.

Since the condition is ordinarily rather benign in its clinical manifestation, and is generally quite amenable to effective treatment, its importance would seem, as noted by others,<sup>3, 6</sup> to lie in its recognition. Our case had been told previously that she had congenital heart disease, and an operative note for a pelvic laparotomy mentioned the unusual color of the blood, but apparently only

in passing. As we have mentioned above, there was a striking absence of any grossly observable cardiorespiratory distress in our patient, despite the obvious coloration, with no finger clubbing, and with negative examination of heart and lungs both by physical examination and by x-ray and electrocardiogram. These observations certainly point up the fact that recognition is nine tenths awareness

TABLE 1

Family Member	* Methemoglobin, %
Parents of Index Case	1
L. D.	1
J. D.	0
Index Case* and Siblings	
* M. Q.	25
K. D.	35
C. D.	2
L. S.	1.5
L. A.	2
M. M.	25
C. H.	24
Progeny of Index Case and Siblings	
* M. Q.	
O. Q.	1
D. Q.	2
C. D.	
C. D.	1.5
L. D.	1.5
L. S.	
L. W. S.	1
R. S.	1
W. S.	1.5
J. H. G.	1.5
P. M.	1
G. S.	1
M. A. S.	1
B. S.	2
L. A.	
N. S.	1.5
G. A.	.5
M. A.	2
C. H.	
R. M. H.	.5
E. H.	0
M. H.	0
S. H.	0

2% methemoglobin or less is assumed to be within normal limits.

\* Methemoglobin was determined by the method of Horecker and Brackett, *J. Biol. Chem.* **152**: 669, 1943. Instead of a Coleman spectrophotometer, a model 14 Cary spectrophotometer with 1.0 cm. cells was used. Absorbance was measured at 815 m $\mu$  after the addition of potassium ferricyanide.

of the condition. Establishing the diagnosis is relatively simple, and various methods have been described by several authors.<sup>4, 5</sup> In our case, a sample of arterial blood was obtained which had a grossly abnormal, purplish black color. The addition of a few drops of potassium cyanide immediately changed the color. Subsequently, the more elaborate process of spectroscopic examination substantiated the impression.

## SUMMARY

A case of familial congenital methemoglobinemia is reported, along with a study of the family. A discussion of the nature of the condition, genetic aspects observed in this case and its recognition is presented. The authors feel that awareness of this condition is important in its recognition, and that such awareness may be stimulated by the reporting of a rather unusual disease out of a clinical practice in a smaller community.

## ACKNOWLEDGMENTS

We are indebted to Dr. William J. Klerk, of Kalamazoo, Michigan, for allowing us to see and study this case.

We wish to express our gratitude to Mr. J. E. Stafford, of the Department of Physical and Analytical Chemistry of the Upjohn Company Research Laboratories, for his help in performing all of the spectroscopic analyses of the blood specimens.

We are further indebted to Bronson Methodist Hospital, Kalamazoo, Michigan, for making possible the study of the index case in the hospital, and for sponsoring the field trip to study the other members of the reported family.

## SUMMARIO IN INTERLINGUA

Es reportate detaliate un caso de congenite methemoglobinemia familial. Le detection de iste caso permitteva al autores constatar le mesme condition in tres frateros e instigava un studio de familia. Es presentate le arbore genealogic de iste familia pro tres generationes. Al tempore de su detection, le caso initial illustrava le satis typic confusion diagnostic con cogenite morbo cardiac cyanotic. Es sublineate le aspecto characteristic de coloration anormal que suggere intense grados de cyanosis in despecto de normal constatationes cardiovascular e pulmonar. In un investigation detaliate, le sol constatation significative deviate ab le norma esseva, a parte le concentration de methemoglobina, un leve hyperplasia del medulla ossee.

Es presentate un revista del theorias currente—specialmente illos de Breaky, Gibson, e Harrison—con respecto al pathophysiologia de congenite methemoglobinemia. Isto include un description del systema enzymatic que es responsabile pro le reduction de methemoglobina a hemoglobina con contento de ferro in forma ferrose in despecto del continue tendentia oxydatori in le presentia de oxygeno. Le hic proponite conception de ille mechanismo presuppone un deficiente activitate de diaphorase I. Le differente medios per le quales blau methylenic e acido ascorbic corrige le aberration es discutate super le base del supra-mentionate theoria.

Le autores commenta le usualmente benigne natura del condition e sublinea le importantia de su recognition.

Es presentate un discussion del aspectos genetic de methemoglobinemia, signalante le manco de accordo con respecto al question del dominantia o recessivitate del character. In iste connexion, le transsaltation de un generation in le arbore genealogic del autores es notate. In plus, le constantia del contento de methemoglobina in le casos presentate pare indicar un constantia del defecto in un familia particular.

Le autores opina que per reportar iste casos ab lor experientia clinic in un micre communitate illes stimula lor collegas a prestar attention a iste condition.

## BIBLIOGRAPHY

1. Lee, M. H., and Jolly, H.: Severe congenital methemoglobinaemia in an infant, *Lancet* 2: 1147 (Dec. 7) 1957.
2. Dine, M. S.: Congenital methemoglobinemia in newborn period, *Arch. Dis. Childhood* 92: 17 (July) 1956.

3. Breaky, V. K. St. G., Gibson, Q. H., and Harrison, D. C.: Familial idiopathic methaemoglobinaemia, *Lancet* 1: 935-938 (Apr. 28) 1951.
4. Baikie, A. G., and Voltis, D. J.: Gas transport function of the blood in congenital familial methaemoglobinaemia, *Brit. M. J.* 2: 73-76 (July 10) 1954.
5. Cartwright, G. E., in *Harrison's Principles of internal medicine*, 2nd Ed., 1954, The Blakiston Company, New York, pp. 1290-1292.
6. Gasul, B. M., Fell, E. H., Casas, R., and Pereiras, R.: Congenital methemoglobinemia simulating tricuspid atresia, *J. A. M. A.* 149: 258-260 (May 17) 1952.
7. Korver, H.: Zyanose durch familiäre Methämoglobinämie, *Arch. Kinderh.* 146: 231, 1953.
8. Codounis, A.: Hereditary methaemoglobinaemic cyanosis, *Brit. M. J.* 2: 368-371 (Aug. 16) 1952.

### CHRONIC RADIATION NEPHRITIS: A REVIEW OF THE LITERATURE WITH REPORT OF A CASE \*

By JAMES A. JERNIGAN, Lt. Col., USAF (MC), F.A.C.P., *Washington, D. C.*

CHRONIC radiation nephritis is a distinct clinical entity that is mentioned infrequently in the textbooks and journals of internal medicine. For example, a case report or article on the subject has not appeared in the *Annals of Internal Medicine* dating back to volume I in 1927. The latest edition of the *Physician's Handbook*<sup>1</sup> does mention radiation nephritis as one of the causes of hypertension. As deep radiotherapy grows more popular, with high-energy beams from linear electron accelerators, other supervoltage x-ray machines, radioactive sources, and the use of conventional therapy units, the internist should be familiar with the renal complications from radiation.

Experimental radiation nephritis was first defined in 1904 by Linser and Baermann.<sup>2</sup> In 1905 Schulz and Hoffman<sup>3</sup> confirmed these findings in animals. Later, in this country, Hartman, Bolliger and Doub<sup>4</sup> showed that both acute and chronic nephritis could be produced in dogs by radiation. This work, and their subsequent experiments,<sup>5,6</sup> closely resembled the clinical and pathologic findings which were recognized years later in humans. Despite these excellent experiments, there remained a widespread belief for many years that renal tissue was markedly insensitive to irradiation damage. This erroneous impression was due to many reports on experiments which used animals that were not followed long enough, and also to the fact that basic and valid research was "lost in the literature." Paterson,<sup>7</sup> in his report on renal damage from radiation, states that he would have been more cautious if he had known of the previous work.

The basic process leading to the histopathologic changes in the kidneys or other organs following irradiation has not been fully clarified. Patt<sup>8</sup> presents the most widely accepted theory—that is, that radiation dissipates in the tissue by releasing electrons in the atoms through which it passes. This process of ionization causes molecular changes. The cell metabolism is altered, and this

\* Received for publication June 20, 1958.

From the Department of Internal Medicine, 3810th U. S. Air Force Hospital, Maxwell Air Force Base, Alabama.

Requests for reprints should be addressed to James A. Jernigan, Lt. Col., Aviation Medicine Clinic, 4A-750, Pentagon, Washington 25, D. C.

eventually results in histopathology. Thus, physical energy (radiation) is converted to a chemical equivalent (ionization), and histologic changes (pathology) follow.

The early and late effects of radiation on the kidneys have been clarified in experiments by Warren.<sup>9</sup> Hyperemia is noted in the early days and weeks after exposure. This is followed in weeks or months by swelling and desquamation of the tubules. The proximal convoluted tubules appear to be most sensitive. In the subsequent months there is marked tubular degeneration, with little sign of regeneration. Later, hyalinization of the glomeruli and interstitial fibrosis develop. Endarteritis and intimal proliferation of all vessels are the last histopathologic changes to appear, and may occur 12 or more months after irradiation. There is no pathognomonic sign on gross or microscopic examination, but the increase in interstitial fibrosis is constant and characteristic. The ureters are relatively more resistant. However, stenosis may occur from fibrosis in the wall and epithelial injury. The recent report by Cogan and Ritter<sup>10</sup> on renal biopsies in two patients with radiation nephritis suggests that the glomerulus is the portion of the kidney primarily affected. However, they also found degenerative cellular changes and intercellular fibrosis. Certainly more renal biopsies in humans with early and minimal radiation nephritis will be needed to clarify just what part of the kidney in man is most sensitive.

The first large number of patients with radiation nephritis was reported by Kunkler, Farr and Luxton.<sup>11</sup> Twenty-two out of 55 patients irradiated for seminoma developed renal damage six to 18 months after therapy. Seven of the 22 patients died from the complications of hypertension or renal insufficiency 12 to 25 months after the nephritis had become evident clinically. Of the 15 patients who survived, only two had no evidence of renal damage at the end of the follow-up period. This period ranged from 15 to 54 months after the nephritis appeared. The more common symptoms pointing to nephritis were shortness of breath (14 patients), headache (12 patients), edema (12 patients), and weakness (six patients). The initial findings pointing to radiation nephritis were hypertension, proteinuria, and elevated blood urea nitrogen (mean, 85 mg.%; range, 38 to 275 mg.%). Sixteen patients had anemia (hemoglobin range, 4.7 to 13.7 gm.%). Hemorrhagic retinitis was an unfavorable sign, as all three patients with this finding died. Two of three patients with papilledema died, but the other patient was well 39 months later and showed only a mild hypertension of 150/100 mm. of Hg. Transfusions and general supportive measures appeared to be the only useful therapy. Later, Luxton<sup>12</sup> reported on 27 patients out of 137 treated who developed radiation nephritis. Only five of the 27 died in renal failure. These workers found that radiation nephritis can be expected when 2,300 r or more are given to both kidneys in five weeks. They conclude that the chances of receiving serious renal damage are less if one third of one kidney is outside the field of irradiation, or if less than 2,300 r is delivered to the kidneys. The importance of evaluating kidney function and location prior to heavy radiotherapy in the kidney region is evident.

Other significant contributions include case reports on patients with unilateral radiation nephritis.<sup>10, 13, 14</sup> All three patients had severe hypertension and were cured by nephrectomy. This illustrates the importance of careful evaluation of both kidneys even after radiation nephritis appears. Among other case reports on radiation nephritis, there are few contributions on therapy.

Exceptions are the references to experience in pediatric therapy.<sup>15, 16</sup> Children appear to have kidneys which have about the same degree of sensitivity to radiation as do those of adults. The benefit from steroids, antitensives and other drugs, whether used therapeutically or prophylactically, remains to be decided by experimental and clinical observation.

The following case report describes the events leading to uremia and hypertension in a patient who received 3,000 r to both kidneys.

#### CASE REPORT

A 39 year old white housewife first entered the 3810th USAF Hospital, Maxwell Air Force Base, Alabama, in December, 1955, with a diagnosis of pseudomucinous cystadenoma of the right ovary with peritoneal, omental and liver implants. The diagnosis was made when a laparotomy for a pelvic mass was performed at Williams Air Force Base, Arizona, in November, 1955.

In the past history the patient had had uneventful full-term pregnancies in 1946, 1948 and 1950. An uncomplicated appendectomy had been performed in 1950. The family and social history was not remarkable.

The present illness apparently began in April, 1955, when the patient developed pain and swelling in her wrists and hands. Examination showed that the wrists were swollen and tender, and had limited motion. The physical examination, including a pelvic examination, was recorded as "otherwise not remarkable." Blood pressure was 130/80 mm. of Hg. The hemogram, urinalysis, chest and wrist x-rays, and the electrocardiogram were normal. The sedimentation rate was 46 mm. per hour (Wintrobe). The patient was treated successfully with aspirin and bed-rest for 10 days. The diagnosis was "probably rheumatoid arthritis." In November, 1955, the signs and symptoms of arthritis in her hands recurred. In addition, mild abdominal distention and a right ovarian mass were noted on examination. Blood pressure was 102/60 mm. of Hg; hematocrit, 42; urinalysis, negative. Exploratory laparotomy at Williams Air Force Base, Arizona, revealed a right ovarian tumor and widespread peritoneal implants. A bilateral salpingo-oophorectomy was performed. In December, 1955, the patient was referred to the 3810th USAF Hospital for further treatment.

On entry the patient was ambulatory and in no acute distress. Ascites and a well healed laparotomy incision were present. Blood pressure was 110/70 mm. Hg. Admission laboratory work revealed: white blood cells, 8,000, with 54% neutrophils and 42% lymphocytes; hematocrit, 36%; hemoglobin, 11.5 gm.%; urinalysis, negative, with specific gravity of 1.022; blood urea nitrogen, 14 mg.%; serum albumin, 4.6 gm.%, and serum globulin, 3.3 gm.%. An intravenous pyelogram and a barium enema were not unusual.

On January 3, 1956, another surgical exploration was performed to see if radical surgery was feasible. The tumor was too widespread to attempt curative surgery, and so only the omentum was removed. A microscopic specimen of an omental implant is seen in figure 1. The patient made an uneventful recovery from the surgery.

On the eighth postoperative day, roentgen therapy was started. Between January 11, 1956, and March 8, 1956, the patient received an estimated 3,000 r tumor dose in 160 treatments. The irradiation was given to the abdomen through four anterior and four posterior portals, 15 by 18 cm. in size, with a 250 kv. therapy unit using a 0.5 mm. copper filter. Chlorpromazine was used to control nausea while most of the therapy was given on an outpatient basis. Gradually the ascites subsided, and no significant symptoms developed during or immediately after the roentgen therapy.

The patient had few complaints until October, 1956, when mild ankle edema, weakness, shortness of breath, cough and headache appeared. These symptoms gradually increased and were associated with nausea and vomiting. In December, 1956, she was admitted for the second time to the 3810th USAF Hospital. On examination the patient was sitting up in bed in acute distress from coughing, vomiting, and shortness of breath. Blood pressure was 210/120 mm. of Hg; pulse, 120; respiration, 24. Right and left heart failure was evident by generalized edema, venous engorgement, cardiomegaly, gallop rhythm, and râles in both lung bases. The fundi showed marked arteriolar spasm but no papilledema, exudates or hemorrhages. Brownish discoloration of the skin over the abdomen and back marked the area of roentgen therapy. The abdomen was distended with an enlarged liver and some

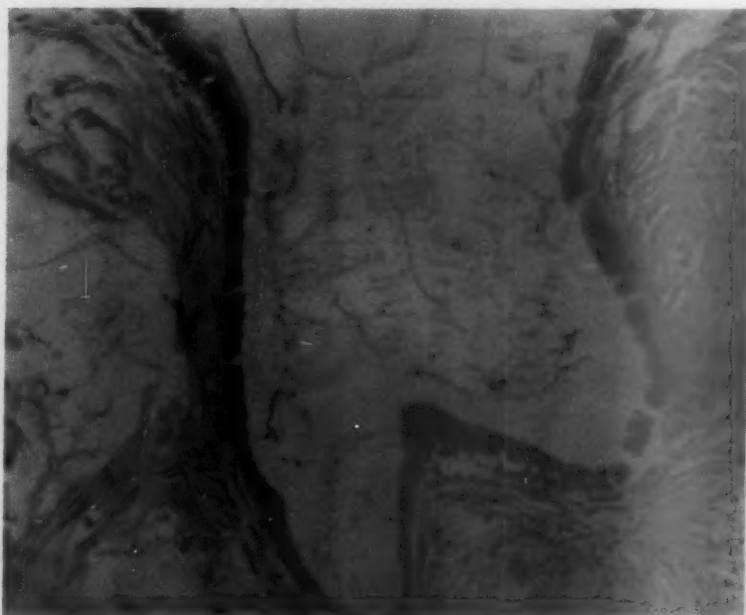


FIG. 1. Omental biopsy showing pseudomucinous cystadenoma. The columnar cells are rather mature and suggest that the metastatic lesion originated from a relatively benign ovarian tumor. Hematoxylin and eosin stain; original magnification  $\times 120$ .

fluid. There was no obvious evidence of recurrent tumor by abdominal and pelvic examination. The neurologic examination was not remarkable. Therapy with morphine, oxygen, reserpine intramuscularly and digitalis intravenously produced marked relief within a few hours.

Laboratory studies on admission revealed a hemoglobin of 8.5 gm.%; hematocrit, 25%; red blood cells, 2.6 million per cubic millimeter; white blood count, 4,800 per cubic millimeter, with 60% neutrophils, 36% lymphocytes and 4% monocytes. A catheterized urine specimen was clear and showed a specific gravity of 1.005, pH of 7.0, and a 3 plus protein. The microscopic examination, a test for sugar, and a culture were negative. Blood studies were as follows: blood urea nitrogen, 52 mg.%; creatinine, 1.9 mg.%;  $\text{CO}_2$ , 17 mEq./L.; sodium, 144 mEq./L.; potassium, 6.0

mEq./L.; chlorides, 108 mEq./L.; calcium, 9.6 mg.%; phosphorus, 4.0 mg.%; albumin 3.4, gm.%; globulin, 2.0 gm.%. Portable chest x-ray showed cardiomegaly and pulmonary congestion. An electrocardiogram showed left axis deviation and low T waves in Leads I, AVL and  $V_{5-6}$ .

During the subsequent weeks of hospitalization, therapy consisted of limited activity, 2.0 gm. salt diet, digitalis, reserpine, hydralazine hydrochloride, transfusions with packed red cells, and chlorpromazine. In addition, prednisone, 40 mg. daily in divided doses, was given for two weeks. This drug was gradually decreased and then stopped after four weeks. Slowly, all symptoms except weakness and facial edema were controlled. Repeat examination of the abdomen and pelvis after the congestive failure subsided revealed no sign of recurrent tumor. The liver returned to normal size. The blood pressure stabilized at 160/90 mm. of Hg. Studies before

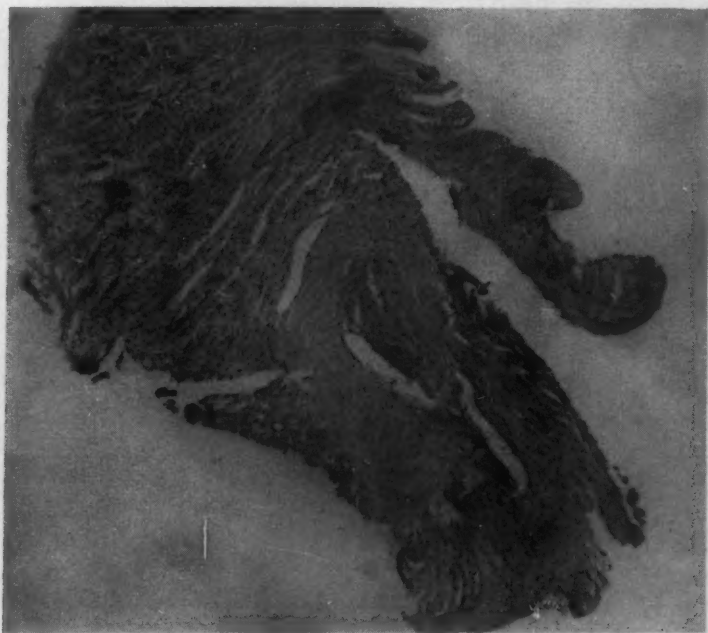


FIG. 2. Kidney biopsy showing increased interstitial fibrosis and intimal proliferation of an arteriole. Hematoxylin and eosin stain; original magnification  $\times 35$ .

the patient's discharge from the hospital in February, 1957, revealed a hemoglobin of 9.5 gm.% and a hematocrit of 30%. Other blood studies were: blood urea nitrogen, 37 mg.%; creatinine, 1.6 mg.%; sodium, 137 mEq./L.; potassium, 5.7 mEq./L.; chlorides, 105 mEq./L.; cholesterol, 270 mg.%. Analysis of a 24-hour urine collection showed a volume of 2.48 L.; specific gravity, 1.016; protein, 0.72 gm.; white blood cells, 1.05 million; red blood cells, 0.5 million, and 4,500 hyaline casts. Repeated urine cultures were negative. An intravenous pyelogram showed faint contrast bilaterally at 10 minutes. No localized abnormality of the genitourinary tract was seen. A phenolsulfonphthalein test showed 15% dye excretion in 15 minutes, 25% in 30 minutes, 40% in one hour, and a total of 60% in two hours. The electrocardiogram remained abnormal, showing nonspecific T wave changes as before.

Bleeding and clotting times were normal. A bone marrow aspiration revealed mild erythroid hyperplasia. The discharge diagnosis was chronic radiation nephritis.

At home, the patient rested for several months before assuming household responsibilities. Digitalis was stopped, but a limited salt intake and reserpine were needed to avoid marked hypertension and edema. A tendency to nocturnal frequency was controlled by reducing the fluid intake in the evening.

At three- to six-month intervals since the patient's discharge from the hospital with radiation nephritis she has had weakness, dyspnea and ankle edema. These symptoms have been associated with a normochromic, normocytic anemia with a hematocrit of 20 to 25%. Symptoms were relieved by transfusions with washed red cells, which raised the hematocrit to about 35%.

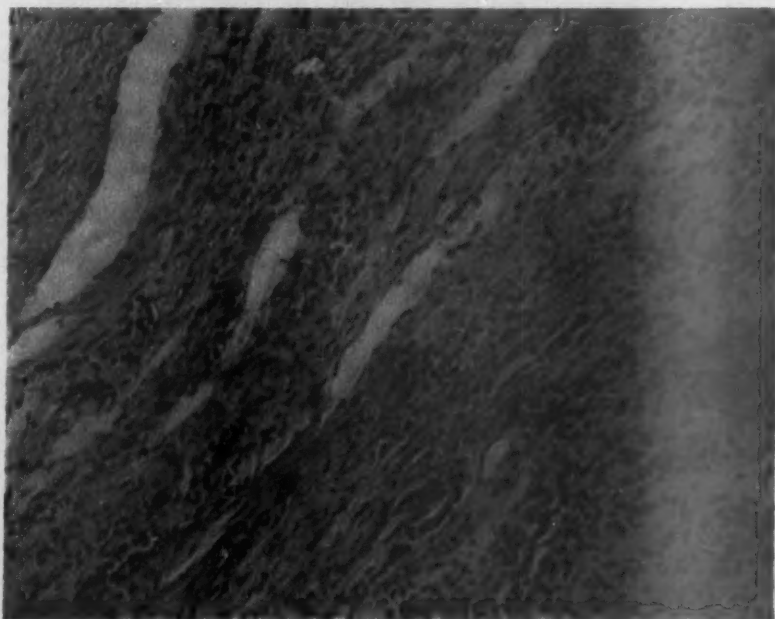


FIG. 3. Kidney biopsy showing increased fibrosis of the interstitial tissue and desquamation of the cells in the tubules. Hematoxylin and eosin stain; original magnification  $\times 120$ .

A renal biopsy was obtained from the left kidney one year after nephritis appeared (figures 2 and 3).

Twenty-five months after the radiation therapy was completed, and 18 months after nephritis appeared, the patient has few complaints. She does all of her housework and has an active social life. The blood pressure remains at 160/90 mm. Hg. The fundi show mild arteriolar spasm without exudate or hemorrhages. The heart and the electrocardiogram remain unchanged from the time of hospitalization. There is no sign of recurrent tumor. The latest laboratory work reveals a clear urine, with specific gravity 1.010, pH of 6, negative test for sugar and protein, and negative microscopic examination. White blood cell count is 6,600 per cubic millimeter, with 52% segmented neutrophils and 48% lymphocytes. Blood chemical studies show: blood urea nitrogen, 49 mg.%; creatinine, 2.6 mg.%; sodium, 140 mEq./L.;

potassium, 6.5 mEq./L.; chlorides, 108 mEq./L.; calcium, 10.2 mg.%; phosphorus, 3.8 mg.%.

#### COMMENT

The need for radiotherapy in this case was debatable. The microscopic picture of mature columnar cells of ovarian origin seen in figure 1 suggests a rather benign process. On the contrary, the gross pathology seen at laparotomy appeared to be very malignant. The physicians in charge chose to use radiotherapy. The five-year survival rate of patients with ovarian carcinomas can be increased significantly by a rather large dose of radiotherapy, according to a review by Sisson and Garland.<sup>17</sup> These authors recommend (a) prompt consultation between surgeon and radiotherapist; (b) bilateral oophorectomy, and in many cases hysterectomy, plus excision of removable omental masses; and (c) early postoperative roentgen therapy to wide fields, supplemented in selected cases by pelvic radium therapy.

The initial signs and symptoms of radiation nephritis which this patient presented were suggestive of malignant hypertension. Symptoms appeared seven months after she received a tumor dose of 3,000 r to the abdomen, including both kidney areas, for metastatic pseudomucinous cystadenoma of the ovary. The negative urine and renal function studies before the irradiation, and the absence of hematuria, pyuria and bacteriuria, are strong evidence against the common types of nephritis. Periarteritis nodosa has not been excluded, but that would represent an unusual coincidence. The renal biopsy produced a limited amount of tissue, as noted in figure 2. Nonspecific changes are seen in the vessels, the tubules and the interstitial tissue. The marked interstitial fibrosis seen in figure 3 is characteristic of radiation nephritis, as described by Warren.<sup>9</sup> Unfortunately, a glomerulus was not obtained in this biopsy, or later, when another biopsy attempt failed. The second intravenous pyelogram, performed after the nephritis appeared, was necessary to exclude unilateral or focal renal disease as a cause of the clinical findings.<sup>10, 13, 14</sup> The amount of radiation received, the latent period and the clinical findings appear sufficient, and beyond reasonable doubt, to diagnose chronic radiation nephritis.

To date, the therapy for the metastatic ovarian tumor has been successful, for the patient shows no sign of recurrence 25 months after treatment. The blood urea nitrogen and creatinine were 37 mg.% and 1.6 mg.%, respectively, in February, 1957. The latest blood urea nitrogen is 49 mg.%, and the creatinine is 2.6 mg.%. This suggests increased renal insufficiency; however, the patient feels better now than a year ago. There is no increase in hypertension, and there is a less frequent need for transfusion. It is obvious that this report covers a relatively short follow-up period. Certainly the prognosis for the patient is very guarded for both the tumor and the nephritis.

#### SUMMARY

Only in the last decade has the sensitivity of the kidney to radiation been widely recognized. If the kidney receives more than 2,300 r in less than five weeks, radiation nephritis can be expected in from six to 18 months.<sup>11</sup> Internists have given this distinct clinical entity relatively little attention.

A review of the history, clinical aspects and histopathology and a case report on chronic radiation nephritis are presented. Further study into the prevention

of radiation nephritis is necessary if patients requiring large doses of radiation to the kidney region are to avoid this complication of therapy.

#### ACKNOWLEDGMENTS

The author is grateful to Mrs. Carrol Gordon for her secretarial aid in preparing this report, and to 1st Lieutenant Earl L. Kinsley for the photomicrographs.

#### SUMMARY IN INTERLINGUA

Chronic nephritis de radiation es un distincte entitate clinic que occurre como complication del therapia radiational. Patientes qui recipe grande doses de radiation al abdomine como tractamento de neoplasmas es candidatos pro iste morbo. Si le renes recipe plus que 2.300 r in minus que cinque septimanas, nephritis per radiation pote esser expectate intra un periodo de tempore de inter sex e 18 menses.<sup>11</sup> Le spectro clinic pote variar inter le extremos de proteinuria transiente e morte per hypertension "maligne." Il existe reportos de patientes con unilateral nephritis de radiation qui requireva nephrectomia. Iste possibilitate require certo un caute evaluation renal si tosto que le presentia del morbo es suspicite.

Le injurias renal es apparentemente le consequentia del proprietates ionisante del radiation.<sup>8</sup> Le ionisation causa alterationes molecular, e in le curso del tempore isto resulta in un alteration del metabolismo e in manifestationes histopathologic. Le precoce e le tardive effectos del radiation esseva describite per Warren.<sup>9</sup> Intra alcun dies il occurre hyperemia del renes. Intra septimanas il occurre desquamation del tubulos. Intra menses il occurre degeneration tubular, hyalinisation del glomerulos, proliferation intimal del vasos, e fibrosis interstitial. Le presentia de fibrosis es le constatacion le plus characteristic, sed il existe nulle signo pathognomonic. Plus frequente biopsias serial del renes in subjectos human va forsan revelar, in le curso del tempore, information additional como Cogan e Ritter lo suggere in lor articulo.<sup>10</sup>

Es reportate le caso de un femina qui recipeva un dose tumoral estimate a 3.000 r in le abdomine como tractamento de un metastatic cystadenoma pseudomucinoso. Le radiation esseva administrate per un machina de 250 kv, con le uso de un filtro de cupro de 0,5 mm, in 160 tractamentos in le curso de un periodo de octo septimanas. Esseva usate quatro portales anterior e quatro portales posterior, omnes de un dimension de 15 per 18 cm. Le areas renal esseva includite in iste portales. Salpingo-oophorectomia bilateral e omentectomy esseva effectuate ante le therapia radiational. Septe menses post le therapia, le patiente disveloppava signos e symptomatos de "hypertension maligne." Signos de nephritis chronic sequeva le successose tractamento de un serie disfallimento congestive initial. Hypertension, leve grados de insufficiencia renal, e anemia ha persistite durante 18 menses de post que le nephritis esseva detegite. Drogas antihypertensive e de tempore a tempore un transfusion de sanguine ha essite le sol requirite mesura de therapia a longe vista. Usque a iste tempore nulle signo de recurrentia del tumor ha essite notate. Un biopsia a agulia in le ren sinistre, effectuate un anno post le apparition del nephritis, monstrava un augmentate fibrosis interstitial, desquamation del cellulas in le tubulos, e proliferation intimal de un arteriola. Le quantitate del radiation administrate, le periodo de latencia, e le constataciones clinic pareva sufficer pro establir con alte grados de certitude le diagnose de chronic nephritis de radiation.

Iste entitate pathologic ha recipite relativamente pauc attention del parte del internistas. Le numero del subjectos exponite a grande amontas de radiation cresce de plus in plus. Assi il deveni necessari pro le medico interessate in le problemas del medicina interne familiarisar se con le complicationes renal del irradiation.

Multo remane a apprender con respecto al historia natural de chronic nephritis

radiational e le methodos de su prevention in patientes qui require grande quantitates de radiation.

## BIBLIOGRAPHY

1. Krupp, M. A., Sweet, N. J., Jawetz, E., and Armstrong, D. C.: Physician's handbook, 9th Ed., 1956, Lange Medical Publications, Los Altos, California, p. 39.
2. Linser, G., and Baermann, H.: Ueber die lokale und allgemeine Wirkung der Roentgenstrahlen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 7: 996, 1904.
3. Schulz, A., and Hoffman, B.: Zur Wirkungsweise der Roentgenstrahlen, *Deutsche Ztschr. f. Chir.* 79: 350, 1905.
4. Hartman, F. W., Bolliger, A., and Doub, H. P.: Experimental nephritis produced by irradiation, *Am. J. M. Sc.* 172: 487-500 (Oct.) 1926.
5. Hartman, F. W., Bolliger, A., and Doub, H. P.: Functional studies throughout the course of roentgen ray nephritis in dogs, *J. A. M. A.* 88: 139-145 (Jan. 15) 1927.
6. Doub, H. P., Bolliger, A., and Hartman, F. W.: The relative sensitivity of the kidney to irradiation, *Radiology* 8: 142-148 (Feb.) 1927.
7. Paterson, R.: Renal damage from radiation during treatment of seminoma testis, *J. Fac. Radiol., London* 3: 270-274 (Apr.) 1952.
8. Patt, H. M., and Brues, A. M.: Nature of biological response to radiation, in *Radiation biology*, Vol. I, Part II, 1954, Hollaender, A., Editor, McGraw-Hill Book Co., Inc., New York, p. 920.
9. Warren, S.: Effects of radiation on normal tissue, *Arch. Path.* 34: 1070-1084 (Dec.) 1942.
10. Cogan, S. R., and Ritter, I. I.: Radiation nephritis (case report number III), *Am. J. Med.* 24: 530 (Apr.) 1958.
11. Kunkler, P. B., Farr, R. F., and Luxton, R. W.: The limit of renal tolerance to x-rays. An investigation into the renal damage occurring following the treatment of tumours of the testis by abdominal baths, *Brit. J. Radiol.* 25: 190-201 (Apr.) 1952.
12. Luxton, R. W.: Radiation nephritis, *Quart. J. Med.* 22: 215, 1953.
13. Dean, A. L., and Abels, J. C.: Study by the newer renal function tests of an unusual case of hypertension following irradiation of one kidney and the relief of the patient by nephrectomy, *J. Urol.* 52: 497, 1944.
14. Levitt, W. M., and Oram, S.: Irradiation-induced malignant hypertension: cured by nephrectomy, *Brit. M. J.* 2: 910, 1956.
15. Mertz, H. O., Howell, R. D., and Hendricks, J. W.: The limitation of irradiation of solid renal tumors in children, *J. Urol.* 46: 1103, 1941.
16. Zuelzer, W. W., Palmer, H. D., and Newton, W. A.: Unusual glomerulonephritis in young children, probably radiation nephritis, *Am. J. Path.* 26: 1019, 1950.
17. Sisson, M. A., and Garland, L. H.: Cancer of the ovary, *Stanford M. Bull.* 15: 191-196 (Aug.) 1957.

## INFECTIOUS MONONUCLEOSIS IN THE AGED \*

By CHARLES M. SHAPIRO, M.D., and HARVEY HORWITZ, M.D., *Chicago, Illinois*

THE occurrence of infectious mononucleosis in patients over 60 years of age has been reported in only four cases.<sup>1-3</sup> The many nonspecific symptoms of individuals in this age group may further complicate the diagnosis of this disease

\* Received for publication July 12, 1958.

From the Department of Hematologic Research and the Department of Medicine, Michael Reese Hospital, Chicago, Illinois.

Requests for reprints should be addressed to Charles M. Shapiro, Captain, MC, Martin Army Hospital, Fort Benning, Georgia.

TABLE 1  
Hematologic Data

	4-17-57	4-20-57	4-21-57	4-24-57	4-29-57	5-6-57	5-13-57	6-18-57	11-19-57	4-21-58
Hemoglobin (gm. %)	11.4		9.7		10.5	10.8	10.8	12.3	14.0	13.6
Red cell count (millions/cu. mm.)	4.1		3.5		3.7	3.7	3.7	4.0	4.6	4.5
White cell count (per cu. mm.)	6,200		9,700		10,000	8,100	9,700	7,000	8,500	9,250
Reticulocytes (per cu. mm.)			72,000			155,000	42,000	40,000	70,000	40,000
Differential count (%)										
Mature polys.	46		51		39	38	41	43	43	52
Immature polys.	19		13		9	5	0	3	4	2
Eosinophils	0		0		0	2	0	1	1	0
Lymphocytes	12		20		32	38	50	38	28	23
Monocytes	23		16		20	17	9	15	24	23
Atypical lymphocytes	1+		2+		1+	1+	1+	None	Rare	None
Spherocytes	None		None		None	None	None	None	None	None
Bone marrow										
		Increase in histiocytes and plasma cells; marked increase in lymphocytes; erythroid to myeloid = 1 to 5.5								
Absorbed heterophil titer				1:160	1:640	1:160	1:80	1:80	Neg.	Neg.
Coombs' test					Neg.					

which, in itself, has protean manifestations. The diagnosis rests on hematologic and immunologic data. Recently we had the opportunity to observe an elderly female who proved to have infectious mononucleosis. It is the purpose of this paper to report her case and to review the relevant literature.

#### CASE REPORT

A 77 year old Caucasian female was admitted to Michael Reese Hospital on April 16, 1957. She stated that she had been well until three weeks prior to admission, when she developed pain in her right hip. At first the pain was noticed only when walking, but shortly thereafter it became continuous. There was no radiation of the pain, and no swelling of the hip was noted. The pain ceased a few days before admission, and at that time a fever of 100 to 103° F. was discovered.

Review of systems was significant only in that the patient had had anorexia during the preceding three to four weeks and had lost an unknown amount of weight.

Physical examination: temperature, 103.6° F.; pulse, 100; blood pressure, 145/95 mm. of Hg; respiration, 36. The eyes, ears, nose and throat were normal. The chest had an increased diameter, but the lungs were clear to auscultation and percussion. The heart was normal. The liver edge was felt three fingerbreadths below the right costal margin. Neither splenomegaly nor ascites could be detected. There was a slight pitting edema over the dorsum of both ankles. No other abnormality was found.

*Laboratory Data:* Urinalysis was normal except for a moderate albuminuria and the presence of occasional white blood cells. Urine culture elicited no growth. Blood chemical tests and electrolyte determinations were normal. Blood cultures were negative on three occasions. A skin test for tuberculosis (purified protein derivative #1) was negative. X-rays of the chest and pelvic girdle were normal. The electrocardiogram revealed a left heart strain pattern.

*Hemogram:* Hematocrit, 36 mm.; hemoglobin, 11.4 gm.%; red blood count, 4,100,000 per cubic millimeter; white blood count, 6,200 per cubic millimeter; sedimentation rate, 32 mm. per hour. Peripheral blood film revealed a monocytosis and a few atypical lymphocytes. There were occasional target cells, but no spherocytes and no polychromatophilia (table 1).

*Liver Profile:* Albumin, 3.0 gm.%; globulin, 3.0 gm.%; bilirubin, 1.1 mg.%; cholesterol, 185 mg.%, with 37% esterified; thymol flocculation, 2 plus; cephalin-cholesterol flocculation, 1 plus; alkaline phosphatase, 9.9 Bodansky units; bromsulphalein retention, none.

The patient continued to have a febrile course and was placed on tetracycline, 1 gm. per day. Parenteral fluids were administered because of persistent nausea and anorexia.

Sternal marrow aspiration performed on the third hospital day revealed a moderate increase in histiocytes and plasma cells, and a marked increase in lymphocytes, mainly mature. The erythroid-myeloid ratio was 1:5.5 (1,000 cells counted).

In view of the abnormal liver studies, the hematologic findings and the unexplained fever, an absorbed heterophil titer<sup>4</sup> was obtained on the seventh hospital day. It proved to be 1:160. Over the ensuing three weeks this titer rose to 1:640 and fell to 1:80. The patient's anorexia disappeared and she became afebrile during this interval.

Although the monocytosis observed on admission had disappeared, the patient had developed an absolute lymphocytosis. She was discharged to convalesce at home.

The patient was seen four weeks after discharge (June 18, 1957), at which time she was asymptomatic, but her heterophil titer was still 1:80, and a mild monocytosis was present. Reexamination five and 12 months later revealed no abnormality. Although the heterophil titer was negative, the monocytosis persisted.

## DISCUSSION

The first report of infectious mononucleosis in a patient over 60 years of age was by Moir in 1930.<sup>1</sup> The patient, a 70 year old male, was seen during an epidemic of "glandular fever" in the Falkland Islands. Heterophil titer determinations were not known at that time.<sup>5</sup> Halcrow et al.<sup>2</sup> in 1943 reported two cases, an 84 year old female and a 64 year old female, observed during an epidemic of infectious mononucleosis. Heterophil titers were elevated, but no absorption studies were done. Recently Fitz-Hugh<sup>3</sup> reported infectious mononucleosis in a 64 year old female with characteristic immunologic findings.

Our patient's initial complaints—hip pain, and fever associated with anorexia and weight loss—suggested to the admitting physician some form of neoplastic disease with metastases. Hepatomegaly and an elevated alkaline phosphatase level were compatible with this diagnosis.<sup>6</sup> However, the decrease in cholesterol esters suggested more diffuse hepatic disease, and the patient was scheduled for a liver biopsy when the elevated heterophil titer was obtained.

Anemia is rarely a complicating factor in infectious mononucleosis.<sup>7, 8</sup> In 1955 Thurm and Bassen<sup>9</sup> reviewed 13 case reports in the literature where hemolytic anemia was associated with infectious mononucleosis, and added two cases of their own. Chernoff and Josephson<sup>10</sup> described an acute erythroblastopenia in a four year old Negro male with this disease. Our patient's hemoglobin level fell from 11.4 gm.% on admission to 9.7 gm.% on the fourth hospital day. The initial blood film revealed the absence of spherocytes and polychromatophilia. A reticulocyte count<sup>11</sup> obtained on the fifth hospital day was 72,000 per cubic millimeter, and by the twentieth hospital day had risen to 155,000 per cubic millimeter. A direct Coombs' test<sup>12</sup> was negative at this time. No evidence of bleeding could be elicited. The data, although not conclusive, suggest that the patient had had a mild erythroblastopenia upon admission, from which she slowly recovered.

Infiltration of the bone marrow with lymphocytes, seen in our patient, has been reported by other authors,<sup>3, 13</sup> but such infiltration is not common.<sup>14, 15</sup> Return of the circulating mononuclear cells to normal levels may require several months or years.<sup>4, 20</sup> Our patient had an initial monocytosis lasting three weeks. Following her discharge from the hospital the monocytosis reappeared and has persisted to the present time.

Heterophil antibodies in infectious mononucleosis may be differentiated from those found in a variety of other conditions by differential absorption with guinea pig kidney and ox red blood cells.<sup>4</sup> Several authors<sup>16-18</sup> have found elevated heterophil antibody titers in leukemia, lymphosarcoma, Hodgkin's disease and other neoplasms, diseases that may have to be considered in the differential diagnosis of infectious mononucleosis. Characteristic absorption studies for the heterophil antibody of infectious mononucleosis were not reported. Feldman and Yarvis<sup>19</sup> reported the case of an 18 year old male whose initial heterophil titer was elevated and showed complete absorption with ox red blood cells and none with guinea pig kidney, findings typical of infectious mononucleosis. Over the ensuing months their patient developed lymphatic leukemia. Although the relationship of these two findings cannot be exactly ascertained, the possibility of two independent diseases occurring at the same time cannot be entirely dismissed.

The abrupt onset of symptoms in our patient, the rise and fall of the absorbed heterophil titer, the paucity of findings on physical examination and the clinical course substantiate the diagnosis of infectious mononucleosis. Despite the persistent monocytosis, the patient remains clinically well 12 months after the initial episode.

#### SUMMARY

The fifth case of infectious mononucleosis in a patient over 60 years of age is presented. Nonspecific findings—fever, abnormal liver function studies, and an increase in circulating mononuclear white blood cells—should alert the physician to seek immunologic tests for this disease before employing more hazardous diagnostic methods.

#### SUMMARIO IN INTERLINGUA

Mononucleosis infectiose es un morbo de manifestationes proteiforme. Ben que commun in plus juvene gruppos de etate, illo es apparentemente rar in ancianos. Solmente quatro previe casos in patientes de plus que 60 annos de etate se trova reportate in le litteratura. Le diagnose se basa super datos hematologic e immunologic.

Un femina de racia blanc de 78 annos de etate se presentava con le gravamines non-specific de dolores coxal, febre, anorexia, nausea, e perdita de peso de plure septimanas de duration. Le examine physic revelava hepatomegalia, e le impression initial esseva que le patiente habeva un neoplasma metastatic. Le hemogramma initial revelava leve grados de anemia e un monocytosis absolute. Studios del function hepatic revelava diffuse morbo hepatic. Iste constatationes stimulava le decision de obtener un determination del titro pro anticorpore heterophile. Iste titro esseva anormalmente alte.

In le curso del sequente septimanas, e con le uso de un therapia solmente symptomatic, le molestias del patiente dispareva; le monocytosis esseva reimplaciate per le presentia de lymphocytos atypic; e le titro pro anticorpore heterophile montava pro retornar subsequentemente a nivellos normal.

Le patiente esseva dimittite ab le hospital pro convalescer a su domicilio. Illa se trova in un stato de eccellente sanitate. Il es interessante notar que su hemogramma, que es normal in onne altere respectos, continua monstrar un monocytosis absolute. Le persistentia de un augmentate numero de cellulas mononucleari in le circulation ha etiam essite notate per altere autores.

Isto es le quinte caso reportate de mononucleosis infectiose occurrente in un patiente de plus que 60 annos de etate.

#### BIBLIOGRAPHY

1. Moir, J. I.: Glandular fever in the Falkland Islands, *Brit. M. J.* 2: 822, 1930.
2. Halcrow, J. P. A., Owen, L. M., and Rodger, N. O.: Infectious mononucleosis, *Brit. M. J.* 2: 443, 1943.
3. Fitz-Hugh, T., Jr.: Acute infectious mononucleosis in a 64 year old woman, *Blood* 12: 398, 1957.
4. Davidsohn, I.: Serologic diagnosis of infectious mononucleosis, *J. A. M. A.* 108: 289, 1937.
5. Paul, J. R., and Bunnell, W. W.: Presence of heterophile antibodies in infectious mononucleosis, *Am. J. M. Sc.* 183: 90, 1932.
6. Ross, R. S., Iber, F. L., and Harvey, A. McG.: The serum alkaline phosphatase in chronic infiltrative disease of the liver, *Am. J. Med.* 21: 850, 1956.
7. Bernstein, A.: Infectious mononucleosis, *Medicine* 19: 85, 1940.

8. Read, J. T., and Helwig, F. C.: Infectious mononucleosis: an analysis of three hundred cases with three characterized by rare hematologic features, *Arch. Int. Med.* **75**: 376, 1945.
9. Thurm, R. H., and Bassen, F.: Infectious mononucleosis and acute hemolytic anemia, *Blood* **10**: 841, 1955.
10. Chernoff, A. I., and Josephson, A. M.: Acute erythroblastopenia in sickle cell anemia and infectious mononucleosis, *Am. J. Dis. Child.* **82**: 310, 1951.
11. Dameshek, W.: A method for simultaneous enumeration of blood platelets and reticulocytes, *Arch. Int. Med.* **50**: 579, 1932.
12. Coombs, R. R. A., Mourant, A. E., and Race, R. R.: A new test for the detection of weak and "incomplete" Rh agglutinins, *Brit. J. Exper. Path.* **26**: 255, 1945.
13. Vogel, P., Erf, L. A., and Rosenthal, N.: Hematological observations on bone marrow obtained by sternal puncture, *Am. J. Clin. Path.* **7**: 436, 1937.
14. Morrison, M., and Samwich, A. A.: Clinico-hematological evaluation of bone marrow biopsies, *Am. J. M. Sc.* **198**: 758, 1939.
15. Limarzi, L. R., Paul, J. T., and Poncher, H. G.: Blood and bone marrow in infectious mononucleosis, *J. Lab. and Clin. Med.* **31**: 1079, 1946.
16. Schultz, L. E.: Heterophile antibody titer in diseases other than infectious mononucleosis, *Arch. Int. Med.* **81**: 328, 1948.
17. Carpenter, G., Kahler, J., and Reilly, E. B.: Elevated titers of serum heterophil antibodies in three instances of monocytic leukemia, *Am. J. M. Sc.* **220**: 195, 1950.
18. Southam, C. M., Goldsmith, Y., and Burchenal, J. H.: Heterophile antibodies and antigens in neoplastic diseases, *Cancer* **4**: 1036, 1951.
19. Feldman, F., and Yarvis, J. J.: Manifestations of hemolytic phenomena and infectious mononucleosis in a case of lymphatic leukemia, *New York State J. Med.* **44**: 1693, 1944.
20. Farley, D. L.: Acute infectious mononucleosis, *M. Clin. North America* **21**: 1139, 1937.

---

### LOCALIZED PRETIBIAL MYXEDEMA: REPORT OF TWO CASES TREATED WITH HYDROCORTISONE BY LOCAL INJECTION \*

By RICHARD W. DYKE, M.D., F.A.C.P., CLAYTON E. WOOD, M.D., and  
SOPHOCLES D. MARTY, M.D., *Indianapolis, Indiana*

REPORTS of successful means of treatment for localized pretibial myxedema are of interest because of its close relationship with progressive exophthalmos, and the possibility that the same agent might likewise reduce progressive exophthalmos. Evaluation of therapy for both conditions must be done with care because of the spontaneous improvement which may occur with both, and because chronic existence of both may be associated with permanent changes from fibrosis.<sup>9, 24, 26</sup>

\* Received for publication July 12, 1958.

Presented in part at the Midwest Regional Meeting of The American College of Physicians, Urbana-Champaign, Illinois, October 12, 1957.

From the Departments of Medicine of Indianapolis General Hospital and Indiana University School of Medicine, and the Department of Dermatology, Indianapolis General Hospital.

Requests for reprints should be addressed to Richard W. Dyke, M.D., Indianapolis General Hospital, Indianapolis 7, Indiana.

First described in the English literature by Watson-Williams in 1895, localized pretibial myxedema has since been discussed frequently by dermatologists and, more recently, by others.<sup>1-18</sup> Research concerning the pathology and biochemistry of the involved tissue, as well as cortical steroid effects on spreading of dyes in the skin as it would apply in this disease, has led to similar investigation of progressive exophthalmos.<sup>19-24</sup> Biochemical tissue analysis and differential staining of retrobulbar tissue from more patients with progressive exophthalmos remain to be done to confirm what appears to be true in the laboratory experiment.

#### CASE REPORTS

*Case 1.* A 31 year old Negro woman, first examined at the Indianapolis General Hospital August 13, 1956, had had a goiter for three months and had noted nervousness, fatigue, weight loss, decreased menses and protruding eyes for six months. Physical examination showed the blood pressure to be 140/60 mm. Hg; pulse rate, 108/min. There was other evidence of hyperthyroidism, as well as prominent eyes, but no signs of progressive exophthalmos. A basal metabolic rate on August 24 was plus 24. On September 6, 1956, antithyroid drug was started. On the same day, two nodular lesions measuring 2 by 3 cm. were noted on the anterior and lateral surfaces of the right leg. These were firm, raised lesions, nonpitting and nontender, with an "orange peel" appearance. Microscopic examination of a biopsy of one of the nodules confirmed the clinical impression of myxedema. On September 27, 1956, hydrocortisone acetate, 12.5 mg., was injected into one of the nodules. By October 11 this had disappeared. A new nodule then appeared on the left anterior leg as well as on the right. Hydrocortisone, 6.25 mg., was injected into each new nodule. These disappeared in approximately one week and have not returned to this date. Exophthalmos has not progressed, and the patient is euthyroid.

*Case 2.* The second patient, a 39 year old Negro woman, was admitted to the Indianapolis General Hospital because of thyrotoxicosis on August 1, 1955. Until the time of her release on August 17, 1955, she complained about nodularity on the lower anterior surface of both legs, and stated that it had been present for several years, with occasional tenderness. Though the nodules were examined at the time, nothing more was done about them. Exophthalmos was present, without evidence of malignant exophthalmos. On July 5, 1956, a clinical diagnosis of localized pretibial myxedema was made and confirmed by biopsy. Two months later her basal metabolic rate, which had been plus 54 and plus 81 prior to antithyroid medication, was minus 30, and there had been a weight gain of more than 40 pounds. Eye signs had not progressed. Cut surface of the biopsy specimen showed a pink, stringy mucous material with a shiny, gray, translucent upper corium. Microscopic examination indicated myxedema of the skin. On November 14, 1956, 8 mg. of hydrocortisone acetate were injected into the leg nodules, which disappeared within two weeks. These nodules measured 3 by 3 cm. and were three in number. There has been no recurrence to date, and the patient is euthyroid.

Localized pretibial myxedema is characterized by lesions of the skin of the lower legs and occasionally of the dorsum of the feet; they are solid, nonpitting, raised, usually nontender yellowish brown or colorless plaquelike nodules, or diffuse, irregular swellings. Involved areas are usually limited to the pretibial area, but diffuse involvement of the entire circumference of the lower legs may occur. Prominent hair follicles are present over the nodules. Burning and itching are frequent complaints. The plaques appear before, during or after the onset of hyperthyroidism. They are frequently associated with progressive

exophthalmos, may appear before it does, and are present in 1.5 to 3% of cases.<sup>9</sup> Clubbing of the fingers, with x-ray evidence of hypertrophic osteoarthropathy, may also be present.<sup>25, 26</sup> Microscopically, there are edema in the dermis, fraying of collagen, splintering of dermal connective tissue elements, stellate-shaped fibroblasts, increased numbers of mast cells and abundant mucin.<sup>9, 40</sup>

#### DISCUSSION

Because of the association of progressive exophthalmos and localized pretibial myxedema, it would seem possible to relate pathogenesis and therapy of the two conditions, even though this association is not present in all cases of either. Curtis<sup>1</sup> and, earlier, Trotter and Eden,<sup>4</sup> incriminated excess thyroid-stimulating hormone activity in the development of exophthalmos, hyperthyroidism and localized pretibial myxedema. The role of exophthalmos-producing substance<sup>27, 28, 29</sup> in the development of localized pretibial myxedema is not clear, but it may indicate that, under its influence, retrobulbar tissue and certain skin areas fail to respond normally to thyroid hormone activity. Recently reported and apparently successful therapy with locally injected triiodothyronine<sup>30</sup> in localized pretibial myxedema would indicate that local tissue factors relating to lack of response to thyroid hormone effect are present. Only temporary softening of the plaques with injection of hyaluronidase indicates failure to remedy the basic defect, even though the tissue in localized pretibial myxedema contains increased levels of hyaluronic acid.<sup>10, 31</sup> Cortical steroids increase spreading in the skin by changing ground substance, and not by increasing effectiveness of hyaluronidase.<sup>19, 23</sup> Local excision, oral and local thyroxine, irradiation of the pituitary for exophthalmos,<sup>6</sup> heat, massage and adrenal cortical hormones by inunction have failed in the treatment of localized pretibial myxedema, as has oral hydrocortisone.<sup>3</sup> Inch and Rolland<sup>17</sup> found local injection of cortisone, with and without hyaluronidase, only temporarily effective, and retrobulbar injection of cortisone for exophthalmos not effective. Perhaps both the localized pretibial myxedema and the exophthalmos had existed long enough that permanent changes from fibrosis were present. Forsey and Anholt<sup>18</sup> used prolonged local injection of hydrocortisone effectively in localized pretibial myxedema.

Watson and Pearce<sup>32, 33</sup> found increased hyaluronic acid, chondroitin sulfate and water content in the nodules of localized pretibial myxedema. Asboe-Hansen<sup>19</sup> and Hayes<sup>23</sup> have demonstrated that, in animals locally injected, cortical steroids will increase the spreading of dye in the skin by altering ground substance. Asboe-Hansen believes there is an accompanying decrease in hyaluronic acid content of the treated connective tissue.

Biochemical changes similar to those described for localized pretibial myxedema have been demonstrated to the satisfaction of some in the retrobulbar tissue of patients with progressive exophthalmos and in animals with experimentally produced exophthalmos.<sup>20, 24, 35-38</sup> Further, administration of cortical steroids causes degeneration of mast cells.<sup>21, 22, 41</sup> Thyrotropin activity increases the number of tissue mast cells and also makes them highly granular (and possibly therefore actively producing mucopolysaccharides); at the same time there is an increase in the tissue content of mucopolysaccharides (hyaluronic acid and its breakdown products). Increased numbers of mast cells in asso-

ciation with increased hyaluronic acid have been demonstrated to be present in myxedematous tissue<sup>9, 24, 40</sup> as well as in retrobulbar tissue in the experimental exophthalmos of laboratory animals.<sup>24, 34, 36</sup> Cortical steroid exhibition produces degeneration of mast cells, with decrease in hyaluronic acid content of tissues.<sup>9, 22, 33, 41</sup> Experimental exophthalmos in the guinea pig is dependent upon the accumulation of large quantities of intercellular ground substance and water in the connective tissue of retrobulbar contents. Mast cells are also increased in numbers. This is similar to the changes observed in localized pretibial myxedema, and suggests a common pathogenesis based upon pituitary hypersecretion.<sup>20, 35</sup> However, Rundle,<sup>42, 43</sup> in studies using autopsy material, has demonstrated in progressive exophthalmos that water and fat-free constituents in retrobulbar contents are increased only in a proportion considered to be normal without producing edema of the extrinsic eye muscles; these muscles were hypertrophied, and accounted for most of the increased bulk in the retrobulbar space. In instances of nonprogressive exophthalmos, increase in amounts of fibro-fatty tissues accounted for the increased bulk. Specific search for mast cells was not mentioned. Rundle also believes that the exophthalmos produced rapidly in the guinea pig is dependent upon edema formation, but implies this is not comparable to the clinical situation. The length of time of the existence of exophthalmos in his patients may have altered early changes. In rats, administration of thyroxin and cortisone did not affect mast cells.<sup>44</sup> Aterman<sup>45</sup> believes that proptosis is the result of a synergistic action of the thyrotropic hormone and an excess of adrenal cortical steroid activity. Smelser<sup>37, 38</sup> found increased water content and fat in retrobulbar tissue of exophthalmos, but later<sup>39</sup> stated that the augmentation of exophthalmos by cortisone would require critical examination of the ideas that an increase in quantity of mast cells and mucoid ground substance in retrobulbar connective tissue causes exophthalmos, and that marked reduction in the numbers of mast cells and quantity of mucoid ground substance is produced by cortisone.

Disappearance of our patients' lesions following local injection of hydrocortisone is predictable from some of the mentioned animal and biochemical studies. Its careful use in progressive exophthalmos may be indicated, although opinions based on clinical and laboratory studies are in conflict. Indeed, although early reports of the results of cortisone therapy systemically for exophthalmos were discouraging,<sup>46</sup> another report has indicated that it may be useful.<sup>47</sup> Perhaps retrobulbar hydrocortisone injection, with resultant higher tissue level, would produce better results.

#### SUMMARY

1. Two cases are reported of localized pretibial myxedema not associated with progressive exophthalmos, with disappearance following local injection of hydrocortisone. These results are predictable on the basis of clinical and laboratory work which has previously established its nature.
2. Study of localized pretibial myxedema leads also to a study of progressive exophthalmos, because of their somewhat frequent coexistence.
3. While some laboratory investigation supports clinical research and the opinion that localized pretibial myxedema and progressive exophthalmos have the same pathogenesis and pathology (and would therefore respond favorably to the same therapeutic agent), other work has not supported this thesis.

4. Examination of the retrobulbar tissue from progressive exophthalmos in more patients for increased numbers of mast cells, hyaluronic acid and water remains to be done.

5. Perhaps retrobulbar injection of hydrocortisone may be indicated, especially in those instances where other methods of therapy for progressive exophthalmos have failed, although this method of therapy is based on conflicting opinion.

#### SUMMARY IN INTERLINGUA

Duo feminas negre con thyrotoxicosis, nonprogressive exophthalmia, e localisate myxedema pretibial esseva tractate con injectiones local de acetato de hydrocortisona a in le lesiones cutanee. Le nodulos del prime del duo patientes dispareva intra un septimana post le injection—in tres sitos—de doses unic de 12,5, 6,25, 6,25 mg del droga, respectivamente. Le secunde patiente habeva etiam tres tal lesiones, e istos dispareva post injectiones unic de 8 mg del droga. Hyperthyroidismo in le duo patientes esseva subjugate facilmente con un droga antithyroide, e le exophthalmia non progrededa. Nulle recurrentia de localisate myxedema pretibial ha occurrite in ulle del casos usque al tempore presente.

Viste que localisate myxedema pretibial e exophthalmia progressive occurre frequentemente insimul in patientes con thyrotoxicosis, il pare plausibile supponer que un methodo successose de tractar le disordine cutanee reducerea etiam le exophthalmia, proque le duo ha probabilemente le mesme pathogenese.

Watson e Pearce trovava in le nodulos de localisate myxedema pretibial, in comparison con pelle normal, augmentate quantitates de acido hyaluronic, sulfato de chondroitina, e aqua. Il existe certe observationes que pare indicar que le histos retrobulbar de patientes con exophthalmia progressive e de animales con exophthalmia pituitariogene de production experimental es characterisate per simile alterations biochimic.

Asboe-Hansen ha demonstrate que le injection cutanee de steroide adreno-cortical altera le substantia fundamental de maniera que le diffusion de un localmente injicite colorante es augmentate. Etiam le contento de acido hyaluronic es reducite in le pelle subicite a ille tractamento. Asboe-Hansen, de accordo con altere autores, crede que le mastocytos del histos que es augmentate sub le stimulo de thyrotropina es le fonte del augmento de acido hyaluronic. Nonresponsivitate local al activitate de hormon thyroide in le histos retro-bulbar e in le pelle es probabilemente responsabile tanto pro exophthalmia progressive como etiam pro localisate myxedema pretibial. Un reporto in le litteratura indica que le injection local de tri-iodothyronina reduce localisate myxedema pretibial. Le tractamento de ambe iste conditiones—exophthalmia progressive si ben como localisate myxedema pretibial—debe esser initiate precocemente, proque ambes pote esser associate con permanente alterationes per fibrosis.

Le supra-mentionate investigationes de base non es completamente foras de controversia. Rundle, in un studio de materiales necroptic, concludeva que exophthalmia progressive non resulta de un augmento del contento de aqua in le histos sed de un augmento del massa muscular. Devitt opina que mastocytos non es afficite per thyroxina e cortisona. Aterman crede que proptosis es un resultado del action synergic de thyrotropina e hormon adreno-cortical.

Un reporto del uso de injectiones retro-bulbar de hydrocortisona signala le facto que nulle reduction esseva effectuate, sed il se tractava in ille reporto de un caso de longe duration. Le administration de hormon adreno-cortical per via oral se ha provate pouco uniforme in le reduction de exophthalmia. Il es possibile que le precoce injection retro-bulbar de hydrocortisona, resultante in un forte concentration in le histos local, effectuarea un reduction del exophthalmia. Viste le supra-

mentonate manco de accordo inter le autoritates, il pare desirabile studiar additionalmente histos retro-bulbar ab casos de exophthalmia progressive con respecto al augmentate contento de aqua e mucopolysaccharido e al augmentate numeration de mastocytos. Si tal augmentos es confirmate, lor presentia supportarea le uso de hydrocortisona per injection retro-bulbar in le tractamento de exophthalmia progressive.

## BIBLIOGRAPHY

1. Curtis, A. C., Cawley, E. P., and Johnwick, E. B.: Association of progressive (malignant) exophthalmos and localized myxedema, *Arch. Dermat. and Syph.* **60**: 318, 1949.
2. Vilanova, X., and Canadell, J. M.: Myxedema circumscriptum thyrotoxicum: report of two cases and remarks on its pathogenesis and treatment, *J. Clin. Endocrinol.* **9**: 883, 1949.
3. Zugerman, I.: Circumscribed pretibial myxedema, *New England J. Med.* **251**: 973, 1954.
4. Trotter, W. R., and Eden, K. C.: Localized pretibial myxedema in association with toxic goiter, *Quart. J. Med.* **2**: 229, 1942.
5. Beierwaltes, W. H.: Clinical correlation of pretibial myxedema with malignant exophthalmos, *Ann. Int. Med.* **40**: 968, 1954.
6. White, R. H. R.: Circumscribed pretibial myxedema, *Guy's Hosp. Rep.* **105**: 205, 1956.
7. French, G. N.: Localized pretibial myxedema, *New England J. Med.* **241**: 299, 1949.
8. Williams, R. H.: Textbook of endocrinology, 1955, W. B. Saunders Co., Philadelphia.
9. Werner, S. C.: The thyroid, 1955, Hoeber-Harper, New York.
10. Underwood, L. J., and Green, W. S.: Pretibial circumscribed myxedema, *Arch. Dermat. and Syph.* **71**: 772, 1955.
11. Cornbleet, T., Barsley, S., and Hoit, L.: Myxedema and localized myxedema, *Arch. Dermat. and Syph.* **71**: 750, 1955.
12. Shumate, A.: Localized myxedema, *Arch. Dermat. and Syph.* **69**: 250, 1954.
13. Morrow, H.: Symmetrical areas of solid edema occurring in Graves' disease, *Brit. J. Dermat.* **11**: 286, 1899.
14. Cohen, E. L.: Myxedema circumscriptum thyrotoxicum, *Brit. J. Dermat.* **58**: 173, 1946.
15. O'Leary, P. A.: Localized solid edema of the extremities in association with exophthalmic goiter, *Arch. Dermat. and Syph.* **21**: 57, 1930.
16. Pillsbury, D. M., and Stokes, J. H.: Circumscribed myxedema of the skin, *Arch. Dermat. and Syph.* **24**: 255, 1931.
17. Inch, R. S., and Rolland, C. F.: Localized pretibial myxedema treated with cortisone, *Lancet* **2**: 1239, 1953.
18. Forsey, R. R., and Anholt, A. W.: Hydrocortisone in the treatment of localized myxedema, *Arch. Dermat. and Syph.* **74**: 352, 1956.
19. Asboe-Hansen, G.: Influence of ACTH and cortisone on dermal spread, *Acta endocrinol.* **9**: 29, 1952.
20. Ludwig, A. W., Boas, W. F., and Soffer, L. J.: Role of mucopolysaccharides in the pathogenesis of experimental exophthalmos, *Proc. Soc. Exper. Biol. and Med.* **73**: 137, 1950.
21. Cavallero, C., and Braccini, C.: Effect of cortisone in the mast cells of the rat, *Proc. Soc. Exper. Biol. and Med.* **78**: 141, 1951.
22. Asboe-Hansen, G.: The mast cell: cortisone action on connective tissue, *Proc. Soc. Exper. Biol. and Med.* **80**: 677, 1952.
23. Hayes, M. A.: The effect of prolonged local treatment with adrenocortical and sex steroids on the intradermal spreading action of hyaluronidase, *Endocrinology* **52**: 646, 1953.
24. Asboe-Hansen, G., and Iversen, K.: Influence of thyrotropic hormone on connective tissue: pathogenetic significance of mucopolysaccharides in experimental exophthalmos, *Acta endocrinol.* **8**: 90, 1951.

25. Thomas, H. M., Jr.: Acropachy: secondary subperiosteal new bone formation, *Arch. Int. Med.* **51**: 571, 1933.
26. McGill, D. A.: A case of thyroid acropachy, *Guy's Hosp. Rep.* **106**: 47, 1956.
27. Dobyns, B. M., and Wilson, L. A.: An exophthalmos producing substance in serum of patients suffering from progressive exophthalmos, *J. Clin. Endocrinol.* **14**: 1393, 1954.
28. Dobyns, B. M., and Steelman, S. L.: The thyroid stimulating hormone of the anterior pituitary as distinct from the exophthalmos producing substance, *Endocrinology* **52**: 705, 1953.
29. Jefferies, W. McK.: Studies of the relationship of the thyrotropic exophthalmic and fat mobilizing principles of pituitary extract, *J. Clin. Endocrinol.* **9**: 927, 1949.
30. Warthin, T. A., and Boshell, B. R.: Pretibial myxedema treated with local injection of triiodothyronine, *Arch. Int. Med.* **100**: 319, 1957.
31. Grais, M. L.: Local injections of a preparation of hyaluronidase in treatment of localized pretibial myxedema, *J. Invest. Dermat.* **12**: 345, 1949.
32. Watson, E. M., and Pearce, R. H.: The mucopolysaccharide content of the skin in localized (pretibial) myxedema, *Am. J. Clin. Path.* **19**: 442, 1949.
33. Watson, E. M., and Pearce, R. H.: The biochemistry of the skin: a review; with particular reference to the mucopolysaccharides, *Brit. J. Dermat.* **59**: 327, 1947.
34. Rose, E.: Endocrine aspects of exophthalmos, *Arch. Ophth.* **56**: 668, 1956.
35. Jefferies, W. McK.: Treatment of exophthalmos from the viewpoint of an internist, *Arch. Ophth.* **56**: 671, 1956.
36. Reese, A. B.: Dacryadenitis in hyperthyroidism, *Arch. Ophth.* **13**: 855, 1935.
37. Smelser, G. K.: Water and fat content of orbital tissues of guinea pigs with experimental exophthalmos produced by extracts of the anterior pituitary gland, *Am. J. Physiol.* **140**: 308, 1943.
38. Smelser, G. K., and Ozanics, V.: The reaction of various types of fat transplanted into the orbit of guinea pigs prior to the development of exophthalmos, *Am. J. Ophth.* **32**: 1557, 1949.
39. Smelser, G. K., and Ozanics, V.: Further studies on the nature of the exophthalmos producing principles in pituitary extracts, *Am. J. Ophth.* **39**: 146, 1955.
40. Allen, A. C.: The skin: a clinicopathologic treatise, 1954, C. V. Mosby Co., St. Louis.
41. Bloom, F.: Effect of cortisone on mast cell tumors (mastocytoma) of the dog, *Proc. Soc. Exper. Biol. and Med.* **79**: 651, 1952.
42. Rundle, F. F., and Pochin, E. E.: The orbital tissues in thyrotoxicosis: a quantitative analysis relating to exophthalmos, *Clin. Sc.* **5**: 51, 1944.
43. Rundle, F. F., Finlay-Jones, L. R., and Noad, K. B.: Malignant exophthalmos: a quantitative analysis of the orbital tissues, *Australasian Ann. Med.* **2**: 128, 1953.
44. Devitt, J. E., Pirozynski, W. J., and Samuels, P. B.: Mast cell resistance to hormonal influence, *Proc. Soc. Exper. Biol. and Med.* **83**: 335, 1953.
45. Aterman, K.: Exophthalmos: its relation to adrenocortical function, *Acta endocrin. Supp.* **10**: 5, 1954.
46. Medical Research Council: Cortisone in exophthalmos: report of therapeutic trial of cortisone and corticotrophin (ACTH) in exophthalmos and exophthalmic ophthalmoplegia by a panel appointed by the Medical Research Council, *Lancet* **1**: 6 (Jan. 1) 1955.
47. Kinsell, L. W., Partridge, J. W., and Foreman, N.: The-use of ACTH and cortisone in the treatment and in the differential diagnosis of malignant exophthalmos: a preliminary report, *Ann. Int. Med.* **38**: 913, 1953.

## PULMONARY PARAGONIMIASIS: REPORT OF A CASE \*

By DONALD H. HARTER, M.D., and STEPHEN I. MORSE, M.D.,  
New York, N. Y.

PULMONARY paragonimiasis has rarely been studied in the United States. The case to be presented, the first admitted to the Columbia-Presbyterian Medical Center, afforded an unusual opportunity for the investigation of this disease, which is found predominantly in the Orient.

## CASE REPORT

A 29 year old Chinese merchant marine officer was admitted to the Medical Service of the Presbyterian Hospital in March, 1956, because of 16 months of cough productive of blood-tinged sputum.

There was no history of parasitic disease or serious illness in any member of his immediate family. In the past the patient had had four episodes of presumed tertian malaria, and an illness compatible with typhoid fever.

As a maritime officer, the patient had been at sea since 1948 and had traveled extensively in the Orient and Near East. In November, 1954, his ship was in the Japanese port of Moji. At that time 35 members of the crew ate fresh-water crabs which had been prepared merely by soaking in salt water. The patient had consumed seven of these during one week. A few days thereafter he noted a pruritic urticarial eruption in the groin, which spread to involve all portions of the trunk and extremities. The rash lasted three days and cleared spontaneously. At the same time the other 34 men also noted a variety of symptoms, including fever, skin eruptions, abdominal pain and cough.

One week after the disappearance of the rash the patient noted the gradual onset of a cough productive of whitish mucoid sputum tinged with small flecks of blood. The cough was not associated with pleuritic chest pain or fever. Eight crew members became seriously ill. Although sputum and stool examinations were negative, blood counts revealed that all of the 35 men had an eosinophilia of 45% or greater. The patient had a white blood cell count of 22,000 per cu. mm., and an eosinophilia of 77%, the highest of the group.

The eight critically ill men were left in Japan, while the remainder of the crew, including the patient, resumed the voyage. Because several men continued to have severe, persistent cough and abdominal pain, medical attention was obtained in India. At that time the patient still had an eosinophilia of 55%. However, examination of numerous sputum and stool specimens failed to reveal infestation with parasites. On the basis of these findings the diagnosis of tropical pulmonary eosinophilia was considered, and three intravenous doses of mapharsen were administered, without effect.

In March, 1956, the patient arrived in New York City. Since there had been no abatement of his cough he reported to a hospital where, on the basis of radiologic evidence, he was told that he had pulmonary tuberculosis. Doubting this diagnosis, the patient visited a clinic of the New York City Department of Health. There, investigation of both sputum and stool yielded the ova of *Paragonimus westermani*.

Admission to the Columbia-Presbyterian Medical Center was advised for further evaluation and management.

\* Received for publication June 2, 1958.

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York, N. Y.

Requests for reprints should be addressed to Donald H. Harter, M.D., Columbia-Presbyterian Medical Center, 622 West 168th Street, New York 32, N. Y.

**Physical Examination:** The patient was an asthenic Chinese male who did not appear to be chronically ill. He coughed frequently, raising large quantities of reddish brown, gelatinous sputum. Temperature, pulse and respirations were normal. There was hyperresonance, and breath sounds were diminished over the right lower lung field. No hepatomegaly, splenomegaly, generalized lymphadenopathy or muscle tenderness was found. Neurologic examination was normal.

**Laboratory Data:** The hemoglobin was 14 gm.%; hematocrit, 42%; erythrocyte sedimentation rate, 56 mm./hr. (Westergren). The white blood cell count was

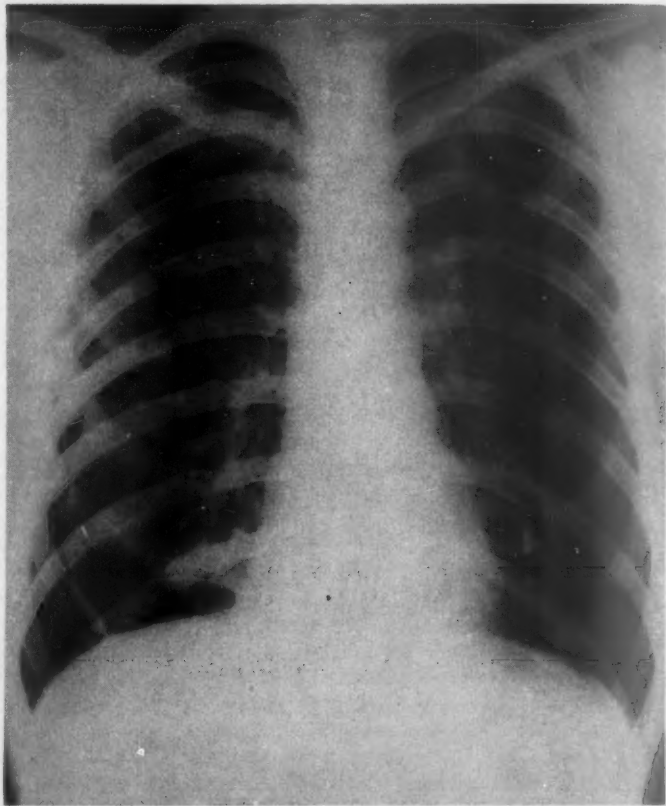


FIG. 1. Chest x-ray at time of admission, revealing nodular densities, cystic lesion in left upper lung, and partial right pneumothorax.

6,000 per cu. mm., with 21% eosinophils. No plasmodial forms were seen. Urinalysis was normal. The Mazzini test was negative. The old tuberculin skin test was positive in 1:10,000 dilution.

Sputum smear revealed numerous operculated eggs of *P. westermani*; no eosinophils, ordinary bacterial pathogens or acid-fast bacilli were demonstrable by direct examination. Culture and guinea pig inoculation were negative for tubercle bacilli.

Eggs of *P. westermani* were found in several concentrated samples of stool. There were no other parasitic elements.

Chest x-ray showed nodular densities in the right middle and left upper lung fields, an oval, cystlike lesion in the left upper lung field, and a partial pneumothorax on the right (figure 1).

There was no laboratory evidence of hepatic dysfunction. Serum electrophoresis showed a hypergammaglobulinemia of 4.0 gm.%, a hypoalbuminemia of 2.9 gm.%, and a total protein of 8.8 gm.%.

After these studies had been obtained the patient was treated with a 25-day course of chloroquine (750 mg./day). Progressive improvement in the severity of

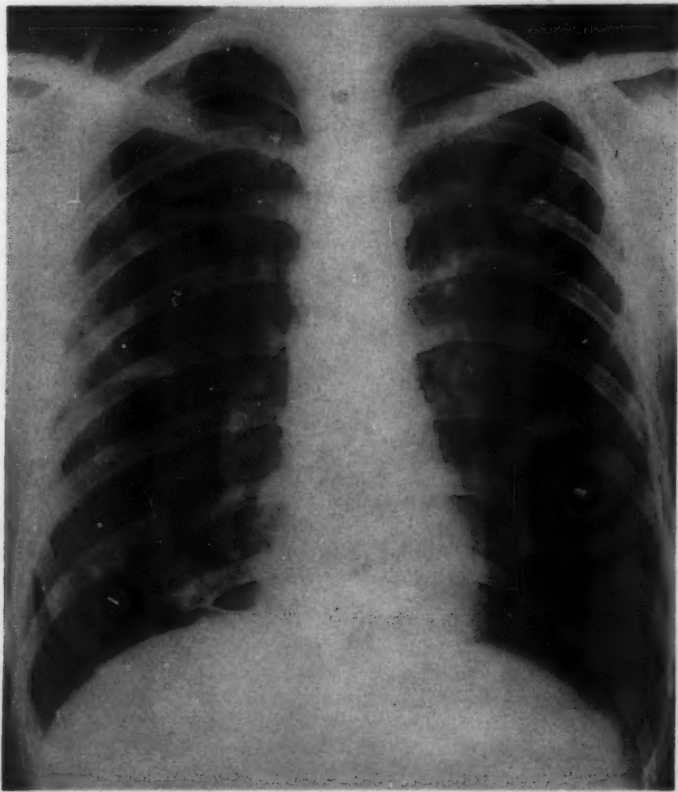


FIG. 2. Chest x-ray following courses of chloroquine and emetine, revealing a diminution of nodularities and pneumothorax.

the cough resulted, and the volume of sputum decreased from 200 ml. per day to 30 ml. per day. There was no change in the number of eggs per milliliter of sputum or in the eosinophilia.

Since there was no further improvement, a course of emetine hydrochloride therapy was instituted, and a total of 270 mg. was administered over a nine-day period. After this, the volume of sputum diminished further and hemoptysis was no longer evident. There was concomitant reduction in the concentration of ova.

Follow-up examination two months later revealed the patient to be in excellent

health. He was producing only 10 ml. of clear mucoid sputum per day without hemoptysis. Physical examination was normal, and there was no anemia. However, an eosinophilia of 23% persisted, and a single degenerated ovum of *P. westermani* was still in evidence on sputum examination. Chest x-ray showed a diminution of the previously described pneumothorax and densities (figure 2). The total protein at this time was 7.5 gm.%, with an albumin of 2.8 gm.% and a gamma globulin of 3.2 gm.%.

One month later, however, the patient's cough had increased and the sputum again contained many eggs. At this time emetine therapy was reinstituted, but the patient did not return to the clinic because of his occupation.

It was learned subsequently that four fatalities occurred in the group of eight men seriously stricken. Two of these resulted from probable cerebral involvement. In the remainder the cause of death is obscure but is presumably related to infection with *P. westermani*.

#### DISCUSSION

The patient's disease occurred in an epidemic setting where the onset of the illness could be easily dated. Of the 35 persons ingesting the raw crabs, all showed initial symptoms of skin eruptions, vague abdominal pains, cough and fever. Four patients eventually succumbed to the disease.

There was a delay of approximately 16 months between the onset of symptoms and the demonstration of ova in the patient's sputum.

Initially, the patient was thought to have tropical pulmonary eosinophilia because of chronic cough, eosinophilia, and pulmonary infiltrates in the absence of a demonstrable etiologic agent. Neither his cough nor eosinophilia responded to arsenical therapy. In Ball's review of tropical pulmonary eosinophilia,<sup>1</sup> pulmonary paragonimiasis is not included in the differential diagnosis of the pulmonary eosinophilias. The data in the present case indicate that pulmonary infiltrates associated with a marked increase in circulating eosinophils may be seen in paragonimiasis.

Later in his course, the patient was thought to have pulmonary tuberculosis. Even in areas of the world where paragonimiasis is commonly seen, it is often confused with tuberculosis. Because of the similarity in symptomatology and radiologic appearance, paragonimiasis should be suspected in any patient from an endemic area who has a chest x-ray suggestive of tuberculosis.

The presence of eosinophilia in patients with pulmonary paragonimiasis has been the subject of some debate. Twelve patients reported by Tillman and Phillips<sup>2</sup> had eosinophilia in the presence of other intestinal parasites, and it was concluded that this was the consequence of organisms other than *P. westermani*. This hypothesis gained support from the report of Roque et al.,<sup>3</sup> who observed that eosinophils disappeared from the blood when treatment was directed at the other helminths. In the present case no other parasites were demonstrated. This suggests that eosinophilia may well be a primary manifestation in paragonimiasis.

Hypoalbuminemia and hyperglobulinemia have been previously described.<sup>2</sup> Electrophoresis of the patient's serum showed the increase in globulin to be specifically localized to the gamma globulin fraction.

The finding of a pneumothorax in pulmonary paragonimiasis is relatively rare. A recent radiologic survey of 80 patients with this disease showed it to be present in only three.<sup>4</sup>

Therapy of paragonimiasis has long been restricted to the use of emetine hydrochloride. Recently, chloroquine has been shown to have the effect of diminishing the sputum volume and concentration of ova when used following partially successful emetine treatment.<sup>6</sup> In the case under discussion, initial use of chloroquine appeared to have some effect. In view of the toxic qualities of emetine, it would appear reasonable to use chloroquine as the drug of first choice. The effect of prolonged use of the drug in paragonimiasis is not fully known, but under such conditions, supplementary emetine might prove to be unnecessary.

#### SUMMARY

A case of pulmonary paragonimiasis acquired in an epidemic setting is described in a 29 year old Chinese merchant seaman.

The diagnoses of tropical pulmonary eosinophilia and pulmonary tuberculosis had been made before the cause of the difficulty became evident. This emphasizes the necessity for considering pulmonary paragonimiasis in persons from endemic areas with infiltrative or cavitary pulmonary disease.

Eosinophilia was found in the absence of other associated parasitic infestation. Associated hyperglobulinemia was localized to an increase in the gamma globulin fraction.

Chloroquine and emetine were employed alternately, with good initial results.

#### ACKNOWLEDGMENT

The authors wish to express their gratitude, for his encouragement and for supplying some of the clinical data, to Howard B. Shookhoff, M.D., Assistant Professor of Tropical Medicine, College of Physicians and Surgeons, and Chief, Division of Tropical Diseases, Bureau of Preventable Diseases, Department of Health, City of New York.

#### SUMMARIO IN INTERLINGUA

Es reportate un caso de paragonimiasis pulmonar, vidite in un chinese officiero del marina mercantil de 29 annos de etate. Le morbo esseva contrahite in un ambiente epidemic. Le patiente esseva un de 35 homines qui mangiava non-cocite crabbas de aqua dulce in un porto de Japon. Omne le 35 homines disveloppava symptommas, e octo deveniva seriemente malade. In le caso del patiente hic reportate, le initial eruption urticarial pruritic esseva sequite per un tusse chronic que produceva sputo a maculation sanguinee. Marcate grados de eosinophilia esseva notate. Un intervallo de circa 16 menses passava inter le declaration del symptommas e le demonstration de ovos de *Paragonimus westermani* in le sputo del patiente. Durante iste intervallo, le diagnose de tropic eosinophilia pulmonari e de tuberculose pulmonari esseva considerate.

Le examine al tempore del admission al hospital monstrava un asthenic chinese mascule qui tussiva frequentemente, producente grande quantitates de sputo gelatinose de color rubi-brun, sed qui non pareva esser chronicamente malade. Hyperresonantia e reducite sonos de respiration esseva constatate in le campo dextero-inferior del pulmon. Le resto del examine physic se teneva intra limites normal.

Le numeration leucocytic esseva 6.000 per mm<sup>3</sup>, con 21% de eosinophilos. Le sedimentation erythrocytic esseva 56 mm per hora (Westergren). Le hemoglobina e le hematocrite esseva normal. Un frottis de sputo revelava numerose ovos operculate de *P. westermani*. Examines de feces concentrate revelava ovos de *P. westermani* in le absentia de altere elementos parasitic. Roentgenogrammas thoracic revelava

densitates nodular, un lesion cystic in le pulmon sinistro-superior, e un partial pneumothorace dextere. Le test cutanee a tuberculina ancian esseva positive a un dilution de 1:10,000, sed bacillos acido-resistente non esseva demonstrate in frottis de sputo, in culturas de sputo, o in le injection de sputo in porcos de India. Le electrophorese de proteina seral demonstrava un hypergammaglobulinemia de 4,0 g pro cento.

Le patiente recipeva un curso de 25 dies de chloroquino (750 mg per die), resultante in un reduction del volumine del sputo sed non in le concentration de ovos. Un curso de hydrochloruro de emetina (270 mg in le curso de un periodo de novem dies) esseva instituite. Isto esseva sequite per un reduction additional del volumine del sputo sed etiam per un reduction del concentration de ovos. Regression radiologic del lesiones pulmonari esseva etiam notate. Le eosinophilos remaneva elevate post le therapia.

Le possibilitate de paragonimiasis pulmonari deberea esser prendite in consideration in personas veniente de areas endemic e exhibiente morbo pulmonari infiltrative o cavitari. Iste possibilitate debe esser prendite in consideration in le diagnose differential de lesiones pulmonari con associate eosinophilia.

Le presentia de eosinophilia in le absentia de parasitos altere que *P. westermanni* in iste patiente suggere que eosinophilia pote ben esser un manifestation primari del morbo.

#### BIBLIOGRAPHY

1. Ball, J. D.: Tropical pulmonary eosinophilia, Tr. Roy. Soc. Trop. Med. and Hyg. **44**: 237-258, 1950.
2. Tillman, A. J. B., and Phillips, J. S.: Pulmonary paragonimiasis, Am. J. Med. **5**: 167-187, 1948.
3. Roque, F. T., Ludwick, R. W., and Bell, J. C.: Pulmonary paragonimiasis: a review with case reports from Korea and the Philippines, Ann. Int. Med. **38**: 1206-1221, 1953.
4. Lee, W. H.: Roentgen diagnosis of pulmonary paragonimiasis, Mem. College Med. Nat. Taiwan Univ. **4**: 23-28, 1955.
5. Chung, H. L., and Hou, T. C.: Chemotherapy of paragonimiasis: further observations on the efficacy of chloroquine, Chinese M. J. **72**: 407-427, 1954.

## EDITORIAL

### CHANGING CONCEPTS OF THE PATHOGENESIS OF WILSON'S DISEASE

For while the tired waves, vainly breaking,  
Seem here no painful inch to gain,  
Far back, through creeks and inlets, making,  
Comes silent flooding in the main.

(Arthur Hugh Clough).

SUCH is progress in medicine, it does not advance evenly upon a broad front but, here or there, surges swiftly forward as a growing point. The internist, daily battling with the more practical problems of care of the sick, inevitably gets left far behind the advancing front and, with the ever increasing volume of medical literature, he can scarce hope to recapture the lost ground. It is only by reading review articles, on these often highly specialized research topics, that he can hope to keep abreast of knowledge and take full advantage of any practical applications that the more theoretical and esoteric conceptions of his research colleagues may have to offer.

Of recent years one of the most active growing points, and one which has an important if limited practical implication, concerns our knowledge of copper metabolism in man. The sequence of events involved has been unusually interesting but one which, it is to be hoped, will become increasingly common in medical research. In this case we start with a rare disease, hepatolenticular degeneration (Wilson's disease). First the clinical and pathological manifestations were recorded<sup>1</sup> then the pathogenesis was investigated and accumulation of copper in the tissues was implicated.<sup>2, 3, 4</sup> At almost the same time a compound able to mobilize trace metals in the body became available in the form of dimercaptopropanol (BAL).<sup>5</sup> The next step was to try this compound in mobilizing copper from the tissues of patients with Wilson's disease and show a therapeutic benefit and this was done by Cumings<sup>6</sup> in London and Denny-Brown and Porter in Boston.<sup>7</sup> Since these important observations were published in 1951, Wilson's disease

<sup>1</sup> Wilson, S. A. K.: Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver, *Brain* 34: 295, 1912.

<sup>2</sup> Haurowitz, F.: Über eine Anomalie des Kupferstoffwechsels, *Hoppe Seyler's Ztschr. f. physiol. Chem.* 190: 72, 1930.

<sup>3</sup> Lüthy, F.: Über die hepato-lentikuläre Degeneration (Wilson-Westphal-Strümpell), *Deutsche Ztschr. f. Nervenhe.* 123: 101, 1931.

<sup>4</sup> Cumings, J. N.: The copper and iron content of brain and liver in the normal and hepato-lenticular degeneration, *Brain* 71: 410, 1948.

<sup>5</sup> Peters, R. A., Stocken, L. A., and Thompson, R. H. S.: British antilewisite: BAL, *Nature, London* 157: 837, 1946.

<sup>6</sup> Cumings, J. N.: The effect of BAL in hepatolenticular degeneration, *Brain* 74: 10, 1951.

<sup>7</sup> Denny-Brown, D., and Porter, H.: The effect of BAL (2,3. dimercaptopropanol) on hepatolenticular degeneration (Wilson's disease), *New England J. Med.* 245: 917, 1951.

has suddenly changed from being a rare condition of academic interest with a hopeless prognosis to become the center of intense research activity and a disease much sought after by those working on the various problems involved. This sequence of events just detailed, description of a new disease, location of the biochemical lesion, postulation of a theoretical treatment, therapeutic trial with demonstrable biochemical and clinical benefit is one of the real, if little known, triumphs of modern scientific medicine.

But when looked at in greater detail and when the more recent chapters are added to the story it becomes at once more like the best kind of detective thriller to which, it is becoming apparent, we have not yet found the correct solution. Up to a point all was plain sailing, copper accumulated in the tissues, BAL mobilized copper, the patients improved; where then are the difficulties implied in the above sentence? The solution of every problem sows the seeds which lead on to the next and in 1949 Holmberg and Laurell<sup>8</sup> did this very thing for Wilson's disease. These two workers isolated and characterized a specific copper binding protein from normal human serum; this protein they named caeruloplasmin because of its characteristic blue color. They showed that it was an alpha globulin with a molecular weight of 151,000 and each molecule carried 8 atoms of copper. While most workers now believe that over 90% of plasma copper is bound to this protein in the normal both Thompson and Watson<sup>9</sup> and Cumings,<sup>10</sup> using a somewhat nonspecific salting out method have found much copper bound to beta and gamma globulins.

Now in patients with hepatolenticular degeneration copper accumulates in most body tissues, particularly the liver and brain<sup>4,11</sup> and is excreted in great excess in the urine<sup>12,13</sup> and it would seem logical to expect some disturbance of copper transport in the blood. Such indeed is the case and Scheinberg and Gitlin<sup>14</sup> were the first to demonstrate a great reduction in the concentration of the blue copper protein, caeruloplasmin, in patients with Wilson's disease. Since this important observation was made in 1952 all workers in this field have agreed that this protein is deficient or absent from

<sup>8</sup> Holmberg, C. G., and Laurell, C. B.: Investigations in serum copper. II. Isolation of copper containing protein and description of some of its properties, *Acta chem. Scand.* 2: 550, 1948.

<sup>9</sup> Thompson, R. H. S., and Watson, D.: Serum copper levels in pregnancy and pre-eclampsia, *J. Clin. Path.* 2: 193, 1949.

<sup>10</sup> Cumings, J. N., Goodwin, H. J., and Earl, C. J.: Blood copper and its relationship to globulins, *J. Clin. Path.* 8: 69, 1955.

<sup>11</sup> Cartwright, G. E., Hodges, R. E., Gubler, C. J., Mahoney, J. P., Daum, K., Wintrobe, M. M., and Bean, W. B.: Studies on copper metabolism. XIII. Hepatolenticular degeneration, *J. Clin. Investigation* 33: 1487, 1954.

<sup>12</sup> Mandelbrote, B. M., Stanier, M. W., Thompson, R. H. S., and Thurston, M. N.: Studies on copper metabolism in demyelinating diseases of the central nervous system, *Brain* 71: 212, 1948.

<sup>13</sup> Porter, H.: Copper excretion in the urine of normal individuals and of patients with hepatolenticular degeneration (Wilson's disease), *Arch. Biochem. and Biophys.* 31: 262, 1951.

<sup>14</sup> Scheinberg, I. H., and Gitlin, D.: Deficiency of ceruloplasmin in patients with hepatolenticular degeneration (Wilson's disease), *Science* 116: 484, 1952.

the blood of almost all patients with Wilson's disease.<sup>15, 16</sup> There is, however, still much disagreement on the significance of this observation. But, whatever the theoretical implications, the finding of a low plasma caeruloplasmin is one of almost diagnostic significance in the detection of Wilson's disease by laboratory methods. In keeping with this deficiency of the copper transport protein, is the finding of a low level of plasma copper. In the normal the concentration varies between 100 and 150  $\mu\text{g}/100\text{ ml.}$ <sup>11, 15, 17, 18</sup> whereas in patients with Wilson's disease the range is mostly between 30 and 70  $\mu\text{g}/100\text{ ml.}$  and more detailed studies have shown that the amount of copper present is out of proportion to the levels of caeruloplasmin; in other words most of the copper present in the blood of these patients is not tightly bound to caeruloplasmin but is loosely complexed to albumin, the "direct reacting copper" of Cartwright.<sup>19</sup> These observations have been synthesized into a theory of the pathogenesis of the disease which can be summarized as follows: Caeruloplasmin production by the body is defective and this is the primary genetically determined abnormality. This in turn leads to an abnormally high concentration of "direct reacting" copper in the blood which is available for diffusing into those tissues with a high affinity for the metal. Once in the tissues the copper ion poisons the enzyme systems leading to cell death, particularly in the brain, liver and renal tubules, thereby producing the classical clinical picture of the disease. This was the leading theory in the field until it suffered a severe blow when fully developed cases of Wilson's disease were described with normal, or near normal, concentrations of caeruloplasmin and it was also observed that there was no correlation between the concentration of this protein and the severity of the patient's illness.<sup>20</sup>

The difficulties in which the caeruloplasmin theory found itself apparently left the field open to its rival which placed the primary abnormality not as an inability to form a copper transport protein in the plasma but to the formation of an abnormal intracellular protein with an increased affinity for the metal. The seeds of this theory were first planted by Uzman and Denny-Brown in 1948<sup>21</sup> and subsequently ably developed by Uzman, with a number

<sup>15</sup> Bearn, A. G., and Kunkel, H. G.: Biochemical abnormalities in Wilson's disease, *J. Clin. Investigation* 31: 616, 1952.

<sup>16</sup> Lahey, M. E., Gubler, C. J., Cartwright, G. E., and Wintrobe, M. M.: Studies on copper metabolism. VII. Blood copper in pregnancy and various pathologic states, *J. Clin. Investigation* 32: 329, 1953.

<sup>17</sup> Bearn, A. G.: Genetic and biochemical aspects of Wilson's disease, *Am. J. Med.* 15: 442, 1953.

<sup>18</sup> Bearn, A. G., and Kunkel, H. G.: Abnormalities of copper metabolism in Wilson's disease and their relationship to the aminoaciduria, *J. Clin. Investigation* 33: 400, 1954.

<sup>19</sup> Gubler, C. J., Lahey, M. E., Cartwright, G. E., and Wintrobe, M. M.: Studies on copper metabolism. IX. The transportation of copper in blood, *J. Clin. Investigation* 32: 405, 1953.

<sup>20</sup> Cartwright, G. E.: Personal communication to the author (see <sup>35</sup>).

<sup>21</sup> Uzman, L., and Denny-Brown, D.: Aminoaciduria in hepatolenticular degeneration (Wilson's disease), *Am. J. M. Sc.* 215: 599, 1948.

of associates, in a series of papers which culminated in the isolation of the abnormal protein itself from the liver of a patient with the disease.<sup>22</sup> According to this theory the deficiency of caeruloplasmin is secondary to the low plasma concentrations of the metal and Uzman<sup>23</sup> apparently no longer believes that the clinical picture is due "to copper intoxication per se." But as in the same publication he also refers to the action of BAL in removing "offending copper" it is difficult to know his exact stand on this point. However, like the caeruloplasmin theory, the intracellular protein theory also has had its difficulties<sup>24</sup> and other workers have not confirmed Uzman's findings. In brain at least, it rather looks, from the work of Folch and Porter,<sup>25</sup> as if there may be a deficiency of the normal intracellular copper proteins, similar perhaps to the caeruloplasmin deficiency in the plasma. Further, the copper chelating peptides in the urine isolated by Uzman and Hood<sup>26</sup> have not been found by Stein, Bearn and Moore.<sup>27</sup>

To date the story right up to date requires mention of some important work with isotopes on copper transport which has gone far to restore the caeruloplasmin theory to precedence. In the normal, radiocopper is absorbed from the gut and appears in the plasma as albumin complexed copper, only to disappear after a few hours and return later bound to caeruloplasmin;<sup>28, 29</sup> whereas in Wilson's disease this sequence of events does not occur, the radiocopper remaining complexed to albumin throughout the period of study. Some work of Osborn and Walshe<sup>30</sup> on Cu <sup>64</sup> uptake by the liver is interesting in this respect, they showed that in normals over 95% of an injected dose of the isotope is concentrated in the liver in 10 hours whereas less than 40% is present in the liver of patients with Wilson's disease by 50 hours. Recently it has been shown that patients with Wilson's disease who have normal concentrations of caeruloplasmin still show an abnormal uptake of radiocopper and they appear to lack the ability to incorporate the metal into their transport protein. As far as

<sup>22</sup> Uzman, L., Iber, P. L., Chalmers, T. C., and Knowlton, M.: The mechanism of copper deposition in the liver in hepato-lenticular degeneration (Wilson's disease), *Am. J. M. Sc.* 231: 511, 1956.

<sup>23</sup> Uzman, L.: The intrahepatic distribution of copper in relation to the pathogenesis of hepato-lenticular degeneration, *Arch. Path.* 64: 464, 1957.

<sup>24</sup> Walshe, J. M.: Hepatolenticular degeneration (Wilson's disease), *Brit. M. Bull.* 13: 132, 1957.

<sup>25</sup> Porter, H., and Folch, J.: Brain copper protein fractions in the normal and in Wilson's disease, *Arch. Neurol. and Psychiat.* 77: 8, 1957.

<sup>26</sup> Uzman, L., and Hood, B.: The familial nature of the aminoaciduria of Wilson's disease (hepatolenticular degeneration), *Am. J. M. Sc.* 223: 392, 1952.

<sup>27</sup> Stein, W. H., Bearn, A. G., and Moore, S.: The aminoacid content of the blood and urine in Wilson's disease, *J. Clin. Investigation* 33: 410, 1954.

<sup>28</sup> Bearn, A. G., and Kunkel, H. G.: Localization of Cu <sup>64</sup> in serum fractions following oral administration: an alteration in Wilson's disease, *Proc. Soc. Exper. Biol. and Med.* 85: 44, 1954.

<sup>29</sup> Earl, C. J., Moulton, M. J., and Silverstone, B.: Metabolism of copper in Wilson's disease and in normal subjects. Studies with Cu <sup>64</sup>, *Am. J. Med.* 17: 205, 1954.

<sup>30</sup> Osborn, S. B., and Walshe, J. M.: Effects of penicillamine and dimercaprol on turnover of copper in patients with Wilson's disease, *Lancet* 1: 70, 1958.

isotope studies are concerned they are indistinguishable from classical cases of the disease.<sup>31</sup>

Very briefly this is the present theoretical basis to our understanding and treatment of the disease. How does it affect the practicing physician and where are the weaknesses as far as he is concerned? Certainly he has now a rational basis on which to build his therapy, that is provided he accepts the hypothesis that the intracellular deposition of copper is toxic to the enzyme systems of the cell. The first and simplest step to take is to exclude food with a high copper content from the diet, such as nuts, chocolate, liver, sea foods, mushrooms and spinach. Second, he can attempt to reduce copper absorption from the gut by giving potassium sulfide, 20 mg. before meals, and third he can try to promote copper excretion from the body. For this he has two principal agents available. Of these BAL has already been mentioned, it has two sulfhydryl groups per molecule which are available for binding copper and given in doses of 200 or 300 mg. daily it will double or even treble the excretion of copper in most cases. Some patients, however, appear to be quite resistant even from the onset and most show a rapidly decreasing cupruresis when treatment is prolonged. Fortunately there is little correlation between the clinical and biochemical response and it has been pointed out by a number of workers that it is difficult to believe the absolute amounts of copper removed from the body are significant.<sup>32</sup> Elsewhere I have stated that the therapeutic action of BAL may be more closely related to the supply of —SH groups for the tissue enzyme systems rather than to the mobilization of copper.<sup>33</sup> The same might well be true for the other, and perhaps preferable therapy with penicillamine.<sup>34, 35</sup> This compound is a simple derivative of the penicillin molecule, dimethyl cysteine, and it probably binds copper by virtue of having both a sulfhydryl and an amino group on the molecule. It can be given by mouth in doses of one or two grams daily and will mobilize very large amounts of copper; cupruresis of up to 4 and 5 mg. a day have been reported.<sup>34, 32</sup> The clinical response to treatment with this compound is slow but steady and it is a mistake to look for a dramatic improvement, though such may occasionally be seen.<sup>35</sup> Like BAL, penicillamine is often associated with a diminishing cupruresis on prolonged treatment and it is not clear if this is due to depletion of a labile copper store or to ability of the body to break the aminoacid down before it has time to chelate the metal. The mode of action of penicillamine is apparently to render plasma copper more diffusible and therefore

<sup>31</sup> Sass-Kortsak, A., Slater, R. J., Geiger, D. G., and Cherniak, M.: A study concerning the basic metabolic defect in Wilson's disease, *Am. J. Dis. Child.* **96**: 540, 1958.

<sup>32</sup> Bearn, A. G.: Wilson's disease: an inborn error of metabolism with multiple manifestations, *Am. J. Med.* **22**: 747, 1957.

<sup>33</sup> Walshe, J. M.: Current views on the pathogenesis and treatment of Wilson's disease, *Arch. Int. Med.* **103**: 155, 1959.

<sup>34</sup> Walshe, J. M.: Penicillamine, a new oral therapy for Wilson's disease, *Am. J. Med.* **21**: 487, 1956.

<sup>35</sup> Fister, W. P., Boulding, J. E., and Baker, R. A.: The treatment of hepatolenticular degeneration with penicillamine, with report of 2 cases, *Canad. M. A. J.* **78**: 99, 1958.

available for excretion at the glomerulus. Following an oral dose of the compound there is a fall in the concentration of copper in the plasma and a corresponding rise in the urine together with an increased renal clearance of the metal in both normals and patients with Wilson's disease.<sup>36</sup> Having postulated that the beneficial action of chelating agents might be due to their ability to supply —SH groups for intermediary metabolism, possibly replacing blocked groups on reduced coenzyme A, Walshe and Hill<sup>37</sup> have now been able to show that 3 days' treatment with penicillamine can correct an abnormality of pyruvate metabolism in two patients with Wilson's disease. After therapy has been stopped, it may take up to 2 weeks before the metabolic abnormality will recur. Perhaps a still more interesting observation is that N-acetyl penicillamine will also correct the abnormal pyruvate metabolism without mobilizing copper from the body, further supporting the view that it is the —SH radicle that is important rather than mobilization of the body stores of excess copper.

Clearly our knowledge of the detailed metabolic processes that are deranged in Wilson's disease are still far from complete and he who thinks otherwise deludes himself. Nevertheless the last ten years have seen the writing of a fascinating new chapter in our understanding of this rare but important genetically determined metabolic disease both as regards pathogenesis and treatment. Maybe it is the highly controversial nature of much of the work and writings on this subject which has kept the field of knowledge so alive and actively advancing.

J. M. WALSHE

<sup>36</sup> Walshe, J. M.: Studies on the action of penicillamine, to be published in *Metal Binding in Medicine*, J. B. Lippincott Company, Philadelphia.

<sup>37</sup> Walshe, J. M., and Hill, L. E.: *Lancet* 2: 444, 1959.

## REVIEWS

*Smoking: The Cancer Controversy.* By Sir RONALD A. FISHER, Sc.D., F.R.S. '47 pages; 22.5 × 14.5 cm. (paper-bound). Oliver and Boyd, Edinburgh, Scotland. 1959. Price, 2s6d.

Probably the most eminent statistician of the period 1920-1950, Sir Ronald Fisher has plunged into the debate on the significance of the association of smoking and lung cancer. Through means of the pamphlet under review, he presents the content of five previously published essays and discusses the issue of inhaling in relation to the interpretation of the smoking-cancer hypothesis.

Dr. Fisher suggests by the use of strong language that the statistically proved association between smoking and lung cancer is far from sufficient evidence to infer that smoking causes lung cancer "... further investigation seems, however, to have degenerated into the making of more confident exclamations, with the studied avoidance of the discussion of alternative explanations of the facts which still await exclusion."

When challenged for alternative interpretations of the statistical association, Dr. Fisher proposes that in view of the nature of evidence involved, it is possible to hypothesize:

1. The effect, cancer is really the cause of the supposed inciting factor, smoking, or
2. Smoking and cancer are coincidentally related and are influenced by a common cause, i.e., the individual genotype.

Although the first of these hypotheses would hardly seem to merit serious attention, the second cannot be cast aside by reasonable thinkers in the area of preventive medicine. It is apparent that other end results, besides lung cancer, appear to be associated with smoking, and one would doubt that a simple causative explanation can be confidently advanced in each instance.

However, the practitioner of medicine, when confronted by a given patient, cannot be a theorist nor does he have the privilege of waiting for a later date when more knowledge may be available. In the light of currently determined facts, he must best advise his patients. On that score he may find it best to have a "working" hypothesis that smoking causes cancer, while alternative concepts are proposed and tested.

This pamphlet is recommended for those who are stimulated by the logic which is applicable to the interpretation of medical statistics. It should be read by investigators working in the lung cancer field.

M. L. T.

*The Clinical Evaluation of New Drugs.* By 14 authors; edited by S. O. WAIFE, M.D., F.A.C.P., and ALVIN P. SHAPIRO, M.D. 223 pages; 16 × 24 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1959. Price, \$7.00.

This is a timely volume written by experts in the field of new drug evaluation. At a time when the clinician is confronted with the decision of accepting or rejecting the avalanche of new drugs which appear on the drug market, this book gives the story of their development.

The treatise is divided into two parts: the first section deals with the principles of drug evaluation and the second part treats of clinical trials of new drugs in practice. In the first part of the book, the problem of new drug evaluation is clearly delineated by one of the editors (S. O. W.). This is followed by an excellent chapter by Dr. Karl H. Beyer, Jr. on the role of pharmacologic investigation in the development of a new drug. What to look for in animal experimentation, how to trace the drug and its metabolites in the animal body, how to evaluate acute and chronic toxicity are discussed in detail in this chapter. The other chapters of Part I deal with the extrapolation of animal data to man, experimental design for drug testing, placebo reactors, statistical analysis of data and the training and attitude of the clinical investigator.

Part II is devoted to clinical trials in various areas of medical practice. For example, the trial of new drugs in infectious diseases, cardiovascular diseases, gastrointestinal disorders and other fields of medicine is discussed. The last chapter of Part II is concerned with the problems of publication, the preparation of the manuscript and the ethics of medical writing.

The book is well written and bids fair to remain an authoritative treatise in this rapidly developing field of medicine.

JOHN C. KRANTZ, JR.

*Elementary Statistics With Applications in Medicine and the Biological Sciences.*

By FREDERICK E. CROXTON, Ph.D., Professor of Statistics, Columbia University. 376 pages; 13.5 × 20.5 cm. (paper-bound). Dover Publications, Inc., New York. 1959. Price, \$1.95.

In the space of 369 pages the author presents a medically oriented outline of elementary statistical technics, a glossary of statistical symbols and an appendix containing fourteen statistical tables. The methodology presented includes a discussion of rates, ratios and percentages; tabular and graphical technics; measures of dispersion and central tendency; correlation; significance tests for measurement data and proportions; and, analysis of variance.

These topics are thoroughly and clearly presented. Each chapter is preceded by a section in which all of the symbols used therein are defined. This appears to be a useful technic for assisting the memory of the occasional user.

Although one may agree with the author's statement that "nearly everyone involved in any aspect of medicine needs to have some knowledge of statistics," there will undoubtedly be differences of opinion concerning the direction and extent of this knowledge. The emphasis in this book is on the analysis of data presumably obtained from well designed investigations. The lack of reference to guide lines in the design of investigations, the pitfalls of biased results and the role of control groups in medical research adds to the misconception that statistical technics are something to turn to after all else has failed.

If this limitation in scope is appreciated this attractive little book can be recommended as a useful addition to the reference shelf of the investigator and the critical consumer of medical literature.

T. F.

*Die Toxoplasmosose bei Mensch und Tier.* By O. THALHAMMER. 307 pages; 17.5 × 25 cm. Wilhelm Maudrich, Vienna. 1957. Price, \$13.75.

The author's stated objective is to present an integrated concept of toxoplasmosis in man and animals. To accomplish this he has reviewed over 1,000 articles in the

world literature and has drawn heavily upon his own experience with toxoplasmosis over a period of more than seven years. The first chapter, an excellent historical review of the major developments in the study of toxoplasmosis, provides the perspective and setting for the subsequent chapters.

A logical sequence of subjects is presented, beginning with a consideration of the organism and ending with discussion of therapy. He appropriately describes in detail the laboratory tests and, in classical German scientific tradition, critically discusses at some length the virtues and defects of the methods. Then, after this consideration of the limitations of the methods upon which available information is based, he develops a unified concept of toxoplasmosis of the fetus and newborn, attempting to explain the variations in clinical manifestations observed on the basis of the developmental state of the fetus at the time at which infection occurs and the stage the infection has attained at the time of birth. The disease as it appears in adults is subsequently presented in some detail. Epidemiology, pathology and pathogenesis are among the many facets considered. Limitations in our knowledge of the story of toxoplasmosis are pointed up at every opportunity. Clinical material and case reports are included to illustrate the concepts being developed. The style is clear and straight-forward. It should present no difficulty to the reader with a reasonable knowledge of scientific German. This book should constitute stimulating reading to all who are interested in toxoplasmosis.

C. L. WISEMAN, JR., M.D.

*Textbook of Pediatrics.* 7th Ed. Edited by WALDO E. NELSON, M.D., D.Sc., with the collaboration of 81 contributors. 1,462 pages; 26 × 18 cm. W. B. Saunders Company, Philadelphia. 1959. Price, \$16.50.

The seventh edition of this fine textbook maintains the excellence of its predecessors. Several good textbooks of pediatrics are available to students in this country, each of them preëminent in certain features, and perhaps the rivalry of authors is a cause of the continuing high quality of these books. Nelson's remains the most popular, and it is still said that the only requirements for certification in this specialty are some experience and a thorough knowledge of all the contents of this book.

A large amount of information has been compressed into only 1,462 pages. The topics discussed include certain general aspects of the care and feeding of well and sick children, prenatal disturbances, the newborn infant, unexpected sudden death, nutritional disturbances, infectious diseases, the digestive tract, the respiratory system, the cardiovascular system, mesenchymal tissues, blood, spleen, lymphatic system, thymus gland, the lipoidoses and reticuloendothelioses, the genitourinary system, the nervous system (tetany, convulsions, mental deficiency, cerebral palsy, behavior problems associated with brain damage), the child with a handicap, psychoses, the endocrine system, metabolic disorders, bones and joints, muscles, skin, burns, allergy, the eye, unclassified diseases, neoplasms, radiation injury, and poisoning. These topics are illustrated well, and the discussions, short as they must be, are still thoughtful, reasonably complete, and, amplified by a few key references, open the way to a deeper study of each subject.

In spite of the increase in knowledge, this work remains a real textbook and not a mere outline or skeleton.

Among many sections that have been modified or rewritten, those on fluid therapy and the nervous system are the most conspicuous, but even here there is less change in outlook than appears. Articles on tropical pediatrics have been added. So also have discussions of the newly recognized inborn errors of metabolism, the newly

recognized viral and fungal diseases, the physiology of respiration, immunization against poliomyelitis, aldosterone and other topics. In spite of these additions the book has fewer pages and less bulk than the sixth edition. This has been accomplished partly by use of finer print, and especially by strict editing, which usually has resulted in increased clarity but occasionally in the loss of an elegant and provocative phrase.

One would like to see one small addition to the section on infectious diseases: a discussion that would help an inexperienced physician to deal with unexplained acute fevers.

The changes in this new edition are evidence that pediatrics is still progressing. As expected, most of the new information is derived from work in genetics, microbiology, chemistry and other fields, rather than pediatrics itself. A sign of progress is the dwindling number of unclassified diseases in successive editions of the book. From four in the fourth edition, the number has decreased to only two in the seventh.

GRANGE SIMONS COFFIN, M.D.

*Heart Disease and Pregnancy: Physiology and Management.* By C. SIDNEY BURRELL, M.D., and JAMES METCALFE, M.D., both of Harvard University, Boston Lying-in Hospital and the Peter Bent Brigham Hospital, Boston, Massachusetts. 338 pages; 16 × 24.5 cm. Little, Brown and Company, Boston. 1958. Price, \$10.00.

In this volume, the authors first describe the maternal adjustments to pregnancy and the general problems of diagnosis, prognosis and management of the pregnant woman with heart disease. They then consider more specifically the common diseases of the heart, congenital and acquired, describing the hemodynamics, recognition and prognosis of these conditions as well as the effect of pregnancy in such patients, and the experience with and the management of such patients.

The authors are widely experienced and their text is authoritative. It is clearly and interestingly written with adequate illustrations, and a good index and a carefully selected bibliography. The point of view is logical, and adequate reference is made to the more recent physiological knowledge of cardiodynamics.

The volume is outstanding in its field and is recommended to internists, cardiologists, and obstetricians.

S. S.

*Nutrition and Atherosclerosis.* By LOUIS N. KATZ, M.D., JEREMIAH STAMLER, M.D., and RUTH PICK, M.D. 146 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1958. Price, \$5.00.

In this text, the authors present a comprehensive review of the rapidly developing field of atherosclerosis research. Over 780 references are included with the emphasis placed on current literature. There are numerous figures from the reports of both the authors and other laboratories. A critical approach is maintained throughout and the analysis appears thorough and scholarly. The authors evaluate present data critically and with candor. Discussed in considerable detail are the epidemiologic, clinical-pathologic and animal experimental findings in nutrition and atherosclerosis. An additional chapter is devoted to hormonal and other endogenous factors related to the problem of atherosclerosis. The final chapter suggests criteria for evaluation of prophylactic and therapeutic regimens of atherosclerotic disease in man, i.e., those which will retard, arrest, and even reverse atherosclerosis and its complications. Finally, the authors make specific recommendations focusing on

dietary prophylaxis aimed at correcting the imbalances in the American diet. These include curtailment of fat, particularly saturated fat; the substitution of fruit for desserts; correction of obesity; reduction of total fat intake with increase in the ratio of unsaturated fats to saturated fats; and the use of lean meats in moderation and the utilization of poultry and sea food in quantity.

This monograph is well written, and provides an excellent review of the literature with the reasoned conclusions reached by an active team in atherosclerotic research.

L. S.

## COLLEGE NEWS NOTES

EDWARD RUTHERFORD LOVELAND

### A SKETCH AND AN APPRECIATION

Edward Rutherford Loveland, B.S.; F.A.C.P. (Honorary), will retire on December 31, 1959 as Executive Secretary of the American College of Physicians, after completing with distinction thirty-three years of continuous and devoted service to the College. "Ed," as he is fondly known by all who are acquainted with him, has contributed so much to the eminence and effectiveness of the College that he will leave behind a mark and a memory which will never be erased.

When Mr. Loveland was appointed to the newly created position of Executive Secretary on April 4, 1926, the College was passing through the most critical period in its history. Dr. Alfred Stengel, serving his first presidential term and committed to a program to regenerate the College, insisted that a qualified lay business executive be appointed. This suggestion was approved by the Regents and, with characteristic good judgment, Dr. Stengel recommended Edward R. Loveland. A wiser and a happier choice could not have been made.

The selection of Mr. Loveland for the exacting duties of Executive Secretary was not haphazard. His academic background, business training, administrative experience and personality were well known to Dr. Stengel. He had come in contact with him frequently in the course of their activities at the University of Pennsylvania, where Mr. Loveland occupied the position of Office and Personnel Manager.

Mr. Loveland was born on July 13, 1893 and spent his boyhood among the farm lands of Southern New Jersey. Here he developed a love for the outdoors which has persisted. He attended the public schools of his native state, later receiving his higher education at Banks College at Philadelphia, The Rochester Business Institute of Rochester, N. Y., the University of Pennsylvania and Temple University, being awarded his B.S. by the latter institution in 1918. He was at various periods between 1912-1921 an Instructor in Commerce at Banks College, Philadelphia, the Wilmington-Delaware High School, the Northeast Philadelphia High School, the West Philadelphia High School and a member of the Faculty of the School of Education at the University of Virginia. When in 1921 he accepted the position of Office and Personnel Manager at the University of Pennsylvania, it became necessary for him to give up teaching, which he had always enjoyed. Mr. Loveland quickly showed his interest in medical administration and educational problems by publishing several papers on these subjects, and in 1923 a well received book entitled "Office Practice."

Mr. Loveland knew little about the College when he became its chief executive officer. It was not long, however, before he became aware of its problems and understood its purposes and ideals. Without delay he undertook his primary responsibility, the establishment of the College Headquarters in Philadelphia and the development of an efficient administrative program. He approached these tasks with the enthusiasm, energy and good judgment which have enabled him to contribute so much to the advancement and prestige of the College.

The casual manner in which the financial affairs of the College were conducted prior to the appointment of an Executive Secretary did not appeal to the business



EDWARD RUTHERFORD LOVELAND

trained Loveland. With tactful determination he proceeded to correct this situation. The excellent financial position presently enjoyed by the College, in large degree, has resulted from his business acumen, conservative management and constant supervision of expenditure.

Early Mr. Loveland came to appreciate the responsibilities and obligations of the College in the broad aspects of graduate medical education. He welcomed the academic implications of his position with its opportunities to develop the educational activities of the organization. This, by constant effort, he accomplished with such success that the Annual Sessions have been progressively improved and expanded; the ever popular postgraduate courses were introduced and developed to a high degree, and the regional meetings steadily bettered in quality and distribution.

One of Mr. Loveland's major interests has always been the *ANNALS OF INTERNAL MEDICINE*—the greatest educational activity of the College. His unfailing coöperation with the editorial staff and publishers along with his able business management have been significant factors in the phenomenal increase in its circulation and volume of advertising.

At the Annual Session of the College at Los Angeles in 1956 the Membership and Board of Regents, as an expression of grateful appreciation of his ability, devoted service to the College and "his constant adherence to the highest traditions of the Medical Profession," made him an Honorary Fellow of the College. Thus, he became the first and only person, other than a physician, to be so honored. About the same time he was elected a member of the Alpha Omega Alpha Honorary Medical Society, an added recognition of his influence upon American Medical Education.

All are in agreement that over his years of service, Mr. Loveland has made a conspicuous contribution to the growth and advancement of the College. It is not only these accomplishments but his personality and force of character as well that have earned him the high regard and great respect of countless Fellows of the College and successive groups of officers, with whom he has invariably coöperated effectively.

The Officers, Regents and the entire Membership of the College contemplate, with sincere regret, the coming retirement of "Ed" Loveland. To him, his associates express their great affection and appreciation for the noteworthy contributions he has made to the College. He will be missed sorely, but the memory of "Ed" Loveland as a man and his achievements will always remain as an inspiration to those who will follow him.

HOWARD P. LEWIS, M.D., F.A.C.P.

President



DR. EDWARD C. ROSENOW, JR.

DR. EDWARD C. ROSENOW, JR., F.A.C.P., TO BECOME EXECUTIVE DIRECTOR OF  
THE AMERICAN COLLEGE OF PHYSICIANS

The Board of Regents of the College announces the appointment of Dr. Edward C. Rosenow, Jr., of Los Angeles, California, as the Executive Director of the American College of Physicians to take office on January 1, 1960. He will succeed Mr. Edward R. Loveland, F.A.C.P. (Hon.) who is retiring on December 31, 1959, after nearly thirty-four years of service as the Executive Secretary of the College.

Dr. Rosenow was born in Chicago in 1909. His family moved to Minnesota in 1915. He holds the degrees of B.A. (1931) from Carleton College; M.D. (1935) from Harvard Medical School, and M.S. (Med.) (1939) from the University of Minnesota, Mayo Foundation. He was an Assistant in Medicine, Mayo Clinic, 1939-40, when he moved to Los Angeles. Here he became an Instructor in Medicine at the University of Southern California, a member of the attending staff of the Los Angeles General Hospital and an associate in the medical department of Huntington Memorial Hospital of Pasadena.

In 1957 he accepted the Executive Directorship of the Los Angeles County Medical Association, but continued as Clinical Professor of Medicine at the University of Southern California, the University of California School of Medicine at Los Angeles, and the College of Medical Evangelists. His appointments in these medical schools provided liaison between the Los Angeles County Medical Society and the schools.

Dr. Rosenow has had a special interest and experience in Postgraduate Medical Education. He was Director of the Medical Extension, University of Southern California; Chairman of the Postgraduate Activities Committee of the California Medical Association and for the past five years has been Editor-in-Chief of *Audi-Digest*.

He is an active member of many medical societies, including the Los Angeles and California State Heart Associations, the Los Angeles Academy of Medicine, the Symposium Society of Los Angeles, the American Heart Association, the California State and American Societies of Internal Medicine and the American College of Chest Physicians. He is Diplomate of the American Board of Internal Medicine and has been a Fellow of the American College of Physicians since 1942. In connection with his Fellowship in the College, he has been a member of the A.C.P. Governor's Advisory Committee for Southern California, he served on one of the Committees of the Los Angeles Annual Session of the College, and has been a member as well as Chairman of the Program Committee of the Southern California Regional Meetings of the College.

He has been President of the Los Angeles Society of Internal Medicine and the Los Angeles Heart Association. He has been a member of the Council and Chairman of the Postgraduate Activities of the California Medical Association, and has served as alternate delegate and consultant to the Medical and Related Facilities Committee of the American Medical Association. He has published a number of scientific papers and has contributed frequently to the programs of the California Medical Association's Postgraduate Institute.

Dr. Rosenow is married and has two children, a son and a daughter, the latter a third-year student at Carleton College. In anticipation of his new duties he moved to Philadelphia in early September in order to spend the remainder of the current year in orienting himself in the work of the College.

HOWARD P. LEWIS, M.D., F.A.C.P.

President

## CERTIFYING BOARD EXAMINATIONS

AMERICAN BOARD OF INTERNAL MEDICINE: Executive Secretary, William A. Werrell, M.D., One West Main Street, Madison 3, Wis. Oral examination in Gastroenterology, Friday and Saturday, March 11 and 12, 1960. Place: Graduate Hospital, Philadelphia, Pa. The closing date for acceptance of requests for admission to examination after approval of applications will be January 15, 1960.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION: Secretary, Earl C. Elkins, M.D., 200 First Street, S.W., Rochester, Minn. Oral and written examinations will be held in New York City, June 17 and 18, 1960. The final date for filing application is February 15, 1960.

## FELLOWSHIPS FOR TUBERCULOSIS RESEARCH

Fellowships and Grants amounting to \$100,000 are being offered by the New York Tuberculosis and Health Association. The Miller Fellowship Grant carries a stipend of \$7,000 to \$10,000, depending on need and is offered to a highly qualified investigator. The Grant will enable him to pursue research work anywhere in the United States in a field of interest to the Association.

Candidates who do not receive the Miller Fellowship may be awarded a fellowship carrying a smaller stipend. New York City area applicants will be given priority. This work must be in medicine, sociology, epidemiology, or the basic sciences, and the project must be conducted in an approved university, hospital, or other institution in the New York City area.

Deadline for application for Fellowships was November 15, while those for grants-in-aid are due at least six months prior to date of the time the contemplated project is scheduled. Forms may be obtained by writing the New York Tuberculosis and Health Association, 260 Park Ave., South, New York 10.

## ANNUAL CONFERENCES ON AGING

The first of four annual conferences on gerontology was held at Duke University, Durham, under the sponsorship of the University's Center for the Study of Aging. Dr. Ewald W. Busse, F.A.C.P., was in charge of the program and was assisted by ten guest speakers from medicine and science.

## NUTRITION EDUCATION SYMPOSIUM

The Commission on Cardiovascular and Metabolic Diseases of the Medical Society of the State of Pennsylvania sponsored a symposium on nutritional and metabolic considerations in disease at Philadelphia October 21, 1959. The program was presented by Drs. Michael G. Wohl, F.A.C.P., Paul Gyorgy, F.A.C.P., Thomas Machella, F.A.C.P., Robert G. Ravdin, all of Philadelphia; William H. Sebrell, Jr., F.A.C.P., and Robert S. Goodhart, both of New York.

## LIBRARY FACILITIES FOR FOREIGN DOCTORS

The Council of the British Medical Association has announced that the Library facilities of the British Medical Association are available to members of Member Associations that hold membership in The World Medical Association.

Foreign doctors who are resident in Great Britain for a period of not more than six months are invited to use the Library facilities of the British Medical Association. They will be afforded all privileges of these facilities with the exception of borrowing the books.

---

A course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital by Drs. Louis N. Katz, F.A.C.P., Richard Langendorf, F.A.C.P., and Alfred Pick. This is an *advanced* course intended only for experienced electrocardiographers. The class will meet daily from 9:00 a.m. to 5:00 p.m., December 7-11, 1959.

Further information and a copy of the lecture schedule may be obtained from the secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

---

#### AMERICAN SOCIETY OF INTERNAL MEDICINE

The Board of Trustees of the American Society of Internal Medicine met on October 30 to November 1, 1959, in Omaha, Nebraska, with the Liaison Committee of the American College of Physicians, to discuss mutual objectives of the two organizations as well as to review scientific and economic developments with representatives of 14 Component Societies of Internal Medicine.

Dr. Robert Wilson of North Carolina, Chairman of the ACP Liaison Committee, discussed the scientific activities of the American College in cooperation with Dr. Wallace M. Yater of Washington, D. C., a member of the Board of Trustees.

Invited to attend the meeting as guests of the ASIM were Dr. Edmond R. Walsh of Omaha, College Governor for Nebraska, and Dr. Joseph D. McCarthy of Omaha, a Regent of the College.

Other invited guests were Dr. Harold M. Neu, President of the Nebraska Society of Internal Medicine, and Dr. William D. Angle, Secretary-Treasurer, both of Omaha.

Dr. Henry J. Lehnhoff of Omaha, a Board member of the ASIM, was in charge of local arrangements.

Included in the program for the meeting was a Progress Report of the Trustees of the American Society by Dr. Clark C. Goss of Seattle, Washington, President; a report on the work of the headquarters office and the present status of dues and budget by Dr. Clyde C. Greene, Jr., of San Francisco, California, Secretary-Treasurer; the plans for the 4th Annual Meeting and discussion of the tentative program by L. Philip Longley, M.D., of Shaker Heights, Ohio; a report on the AMA Regional Conferences on Relative Value Studies by Dr. Stewart P. Seigle of Hartford, Connecticut, President-Elect; proposed changes in ASIM by-laws by Dr. Charles K. Donegan of Miami, Florida; a report on the plans for meeting with representatives of component societies during the Southern Medical Association meeting by Dr. Elbert L. Persons of Durham, North Carolina, immediate Past President, and a discussion of current recommendations of the Board of Trustees by Dr. George K. Wever of Stockton, California.

#### 1960 Annual Meeting of ASIM

The 1960 Annual Meeting of the American Society of Internal Medicine at San Francisco, immediately preceding the Annual Session of the American College of Physicians, will explore the four main purposes of the three-year old society with portions of the program devoted to the scientific, economic, social and political aspects of medicine. All members of the American Society of Internal Medicine and the

American College of Physicians are invited to register and will be provided with reports of activities which previously have been made available only to official delegates of component societies.

Headquarters for the American Society will be the Sheraton-Palace Hotel in San Francisco with the Board of Trustees and Committee meetings scheduled for Thursday, March 31 and Friday, April 1. Program sessions will be held on the mornings of Saturday and Sunday, April 2 and 3, and the House of Delegates will be in session on the afternoons of these same days. Reference Committees will meet Saturday night.

A joint hotel reservation form is being developed in coöperation with the American College of Physicians in order to avoid duplication. All members of the ASIM and/or ACP who wish to be located at the Sheraton-Palace Hotel should so indicate on their housing form when it is received a few months in advance of the meeting.

Special provisions are being made for the interest of the ladies during the ASIM meetings. President Clark C. Goss, M.D., has emphasized to a committee of ladies that he wishes the ladies to feel welcome at the meeting of ASIM and be appropriately provided for in the program of activities. Details of the program will be announced later but the tentative outline—subject to review by the Board of Trustees—is both exciting in its possibilities and suggestive of a most productive two days.

---

The Presbyterian Hospital and Drexel Institute of Technology, both Philadelphia institutions, have received a \$274,000 grant from the National Institutes of Health for research in how medicine, engineering and the physical sciences can coöperate in fighting diseases. The aim of this research will be to expand the use of electronic instruments in combating cardiovascular and other diseases. This joint program will strive to develop teams of medical researchers, physical scientists and engineers who can increase the use of the new technology.

---

#### NEW INDEX WILL SPEED SERVICE TO PHYSICIANS

Beginning January, 1960, a monthly INDEX MEDICUS will be published by the National Library of Medicine. The American Medical Association will publish annually cumulated volumes known as the CUMULATED INDEX MEDICUS.

Subscriptions for the INDEX MEDICUS will be handled by the Superintendent of Documents, Government Printing Office. The CUMULATED INDEX MEDICUS will be sold and distributed separately by the A.M.A.

---

#### FUTURE MEETINGS

##### NATIONAL

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE, INC., Hotel Roosevelt, New York City, Dec. 11-12. Dr. Rollo J. Masselink, 700 W. 168th St., New York 32, Secretary-Treasurer.

NEW YORK HEART ASSOCIATION, Symposium on Salt and Water Metabolism, Biltmore Hotel, New York City, Dec. 11-12. Dr. Alfred P. Fishman, N. Y. Heart Association, 10 Columbus Circle, New York City, Chairman.

AMERICAN ACADEMY OF ALLERGY, Hollywood Beach Hotel, Hollywood-by-the-Sea, Fla., Jan. 11-13. Mr. James O. Kelley, 756 N. Milwaukee St., Milwaukee 2, Wis., Executive Secretary.

AMERICAN ACADEMY OF OCCUPATIONAL MEDICINE, Williamsburg Inn, Williamsburg, Va., Feb. 10-12. Capt. Lloyd B. Shone, Bureau of Medicine and Surgery, Navy Dept., Washington 25, D. C., Secretary.

AMERICAN COLLEGE OF ALLERGISTS, INC., Americana Hotel, Bal Harbour, Miami Beach, Fla., Feb. 28-Mar. 5. Mr. Eloi Bauers, 2160 Rand Tower, Minneapolis 2, Executive Vice-President.

AMERICAN COLLEGE OF RADIOLOGY, Roosevelt Hotel, New Orleans, Feb. 3-6. Mr. William C. Stronach, 20 N. Wacker Dr., Chicago 6, Executive Director.

AMERICAN PSYCHOSOMATIC SOCIETY, Sheraton-Mount Royal Hotel, Montreal, Mar. 26-27. Miss Joan K. Erpf, 265 Nassau Rd., Roosevelt, N. Y., Executive Assistant.

AMERICAN ACADEMY OF NEUROLOGY, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

AMERICAN ASSOCIATION OF IMMUNOLOGISTS, Chicago, Apr. 11-15. Dr. Calderon Howe, Columbia Univ. College of Physicians and Surgeons, New York 22, Secretary-Treasurer.

AMERICAN COLLEGE OF PHYSICIANS, Mark Hopkins & Fairmont, San Francisco, Apr. 4-9. Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Executive Secretary.

AMERICAN GASTROENTEROLOGICAL ASSOCIATION, Roosevelt Hotel, New Orleans, April 1-2. Dr. Wade Volwiler, Dept. of Med., Univ. of Washington, Seattle, Secretary.

AMERICAN PHYSIOLOGICAL SOCIETY, Chicago, Apr. 11-15. Ray G. Daggs, D.Sc., 9650 Wisconsin Ave., Washington 14, D. C., Executive Secretary.

AMERICAN SOCIETY OF INTERNAL MEDICINE, Mark Hopkins Hotel, San Francisco, Apr. 1-3. Mr. Robert L. Richards, 350 Post St., San Francisco 8, Executive Director.

AMERICAN COLLEGE OF CARDIOLOGY, Indianapolis, May. Dr. Philip Reichert, 2709 Empire State Bldg., New York 1, Executive Director.

AMERICAN FEDERATION FOR CLINICAL RESEARCH, Chalfonte-Haddon Hall, Atlantic City, N. J., May 2. Mr. James E. Bryan, 250 W. 57th St., New York 19, Executive Secretary.

AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, Haddon Hall, Atlantic City, N. J., May 1-2. Dr. Saul J. Farber, N. Y. U. College of Medicine, 550 First Ave., New York 16, Secretary.

AMERICAN TRUDEAU SOCIETY, Statler and Biltmore Hotels, Los Angeles, May 16-18. Mr. Frank W. Webster, 1790 Broadway, New York 19, Executive Secretary.

ASSOCIATION OF AMERICAN PHYSICIANS, Haddon Hall, Atlantic City, N. J., May 3-4. Dr. Paul B. Beeson, Yale Univ. School of Medicine, New Haven 11, Conn., Secretary.

NATIONAL TUBERCULOSIS ASSOCIATION, Statler & Biltmore Hotels, Los Angeles, May 15-20. Mr. James G. Stone, 1790 Broadway, New York 19, Executive Secretary.

#### INTERNATIONAL

INTERNATIONAL SYMPOSIUM ON "THE BLOOD PLATELETS," Henry Ford Hospital, Detroit, March 17-19. Shirley A. Johnson, Ph.D., Henry Ford Hospital, Detroit 2, Chairman.

INTERNATIONAL CONGRESS OF GASTROENTEROLOGY, Leyden, Netherlands, Apr. 20-24. Dr. C. Schreuder, 16 Lange Voorhour, The Hague, the Netherlands, General Secretary.

ASIAN-PACIFIC CONGRESS OF CARDIOLOGY (SECOND), Melbourne, Australia, May 23-28. Dr. A. E. Doyle, Alfred Hospital, Melbourne, S. 1, Victoria, Australia.

PAN AMERICAN MEDICAL ASSOCIATION CONGRESS, Mexico City, May 2-11. Dr. Joseph J. Eller, 745 Fifth Ave., New York 22, Director General.

INTERNATIONAL CONGRESS OF CLINICAL PATHOLOGY, Madrid, Spain, June 13-17. Dr. J. Aparicio Garrido, Sandoval 7, Madrid, Spain, Secretary-General.

INTERNATIONAL CONGRESS OF ENDOCRINOLOGY, Copenhagen, Denmark, July 18-23. For information address: Dr. Henry H. Turner, 1200 N. Walker, Oklahoma City 3, Okla., U. S. A.

INTERNATIONAL CONGRESS ON GOITER, London, England, July 6-8. For information write: Dr. John C. McClintock, 149½ Washington Ave., Albany, N. Y., U. S. A.

INTERNATIONAL CONGRESS ON OCCUPATIONAL HEALTH, Waldorf-Astoria, New York, N. Y., U. S. A., July 25-29. Dr. Leo Wade, 15 West 51st St., New York, N. Y., U. S. A.

VITH INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Basel, Switzerland, August 24-27, 1960. Prof. Dr. H. Ludwig, Steinentorstrasse 13, Basel.

INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, sponsored by the Council on International Affairs, American College of Chest Physicians, Vienna, Austria, Aug. 28-Sept. 1. Mr. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Executive Director.

### PERSONAL NOTES

Dr. Louis N. Katz, F.A.C.P., Director of the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, spoke on the "Performance of the Heart" at the meeting of the American Heart Association in Philadelphia in October.

---

Dr. Frank R. Menne, F.A.C.P., formerly Professor of Pathology and Head of the Department of Pathology at the University of Oregon Medical School, Portland, has retired and is now living at Peebles, Wis. Dr. Menne has been a Fellow of the College since 1925.

---

The following members of the College were guest speakers at the 24th Annual Convention of the American College of Gastroenterology, held at Los Angeles, Calif., September, 1959: Drs. James N. DeLamater, F.A.C.P., Pasadena, Jerome A. Ecker, F.A.C.P., Santa Barbara, Marvin Fuchs (Associate), Washington, D. C., Edward W. Hauch, F.A.C.P., Pomona, Theodore S. Heineken, F.A.C.P., Glen Ridge, Jacob Lichstein, F.A.C.P., Los Angeles, Lester M. Morrison, F.A.C.P., Los Angeles, Paul B. Roen, F.A.C.P., Los Angeles, L. Carl Sanders, F.A.C.P., Memphis, Jerome V. Treusch, F.A.C.P., Beverly Hills, Samuel Weiss, F.A.C.P., New York City, C. Wilmer Wirts, F.A.C.P., Philadelphia, and Leo Gitman, F.A.C.P., Brooklyn.

---

Dr. James W. Haviland, F.A.C.P., Seattle, as of September 1, 1959, resigned as Assistant Dean of the University of Washington School of Medicine. He will devote his full time to the practice of Internal Medicine and to teaching at the University.

---

Dr. Lester R. Dragstedt, F.A.C.P., Chairman of the Department of Surgery, University of Chicago, The School of Medicine, will become Research Professor of Surgery at the University of Florida College of Medicine.

Dr. Howard A. Rusk, F.A.C.P., New York City, and Dr. Edward H. Ryncarson, F.A.C.P., Rochester, Minn., were the Sommer Memorial Lecturers at the 12th Annual Scientific Session of the Northwest Regional Academy of General Practice in Portland. Dr. Roger H. L. Wilson (Associate), San Francisco, was also a speaker at this meeting.

---

Dr. Howard R. Bierman, F.A.C.P., has resigned as Director, Hospital for Blood Diseases and Medical Oncology, and Scientific Director of the City of Hope National Medical Center to enter practice in Beverly Hills, Calif., as a consultant in neoplastic diseases, the leukemias, and blood dyscrasias.

---

Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, was a guest speaker at the 21st midsummer Radiological Conference of the Rocky Mountain Radiological Society.

---

Dr. William T. Thompson, Jr., F.A.C.P., has been named Professor and Chairman of the Department of Medicine at the Medical College of Virginia in Richmond.

---

Dr. John J. Butler, (Associate), has been appointed Director of Medical Education at St. Michael's Hospital, Newark, N. J., and Associate Professor in the Department of Medicine, Seton Hall College of Medicine and Dentistry.

---

Dr. William Likoff, F.A.C.P., has been named Clinical Professor of Medicine at Hahnemann Medical College and Hospital of Philadelphia.

---

Dr. Mayer A. Green, F.A.C.P., has been promoted to Clinical Assistant Professor, Section of Allergy, Department of Dermatology, University of Pittsburgh School of Medicine.

---

Dr. Charles M. Thompson, F.A.C.P., recently received the newly created Trustees' Award for "distinguished faculty service" at Hahnemann Medical College and Hospital of Philadelphia.

---

Dr. Leo H. Crip, F.A.C.P., Pittsburgh, Pa., delivered a paper on "The Management of Chronic Vascular Headache" before the 92nd Annual Meeting of the West Virginia Medical Association at White Sulphur Springs during August.

---

Drs. Edward W. Lowman, (Associate), New York, Joseph L. Hollander, F.A.C.P., William J. Erdman, Jr., II., F.A.C.P., and Robert S. Herzog, F.A.C.P., Philadelphia, have become members of the American Institute of Medical Climatology, the President of which organization is Dr. George Morris Piersol, M.A.C.P., former President and former Secretary General of the College.

According to Dr. Piersol, The American Institute of Medical Climatology is an organization formed several years ago by a group of physicians, physiologists, physicists and others interested in the field of Balneology. It has long been recognized that environmental changes have effect upon the health and behavior of human

beings. The purpose of this organization is to stimulate scientific investigations in this field. Heretofore, widely accepted statements have been based largely upon impressions. The organization sponsors scientific meetings and lectureships which it is hoped will increase the interest of physicians in the important area of climatology.

---

Dr. Frederick G. Scovel, F.A.C.P., arrived back in this country in July after six years in India where he was head of the Medical Department of the Christian Medical College, Lundhiana, Punjab. He has accepted an administrative appointment as Executive Secretary of the Christian Medical Council for Overseas Work at the Interchurch Center, 475 Riverside Drive, New York 27, N. Y.

---

Dr. William H. Perloff, (Associate), Director of the Department of Endocrinology, Temple University School of Medicine, will be in charge of the program, Section on Endocrinology, of the next Congress of the Pan American Medical Association in Mexico City, May 2-11, 1960.

---

Dr. Wilhelm Raab, F.A.C.P., Professor of Experimental Medicine, University of Vermont College of Medicine, presided over a Symposium on Catecholamines which was held at the University of Vermont during August, 1959.

---

Dr. John H. Talbott, F.A.C.P., College Governor for Western New York, has been appointed Director of the Division of Scientific Publications and Editor of the *Journal of the American Medical Association*, beginning October 20, 1959.

---

The American Gastroenterological Association has elected the following Officers for 1959: President—Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, Mich.; President-Elect—Dr. Hugh R. Butt, F.A.C.P., College Governor for Minnesota, Rochester; Vice President—Dr. Franz J. Ingelfinger, F.A.C.P., Boston; Treasurer—Dr. G. Gordon McHardy, F.A.C.P., New Orleans, and Secretary—Dr. Wade Volwiler, Seattle.

---

Dr. William H. Perkins, F.A.C.P., Professor Emeritus of Medicine, Jefferson Medical College of Philadelphia, retired July 1.

---

Dr. Albert S. Hyman, F.A.C.P., Associate Clinical Professor of Medicine, New York Medical College, was elected President for 1959-60 of the American College of Sports Medicine.

---

Dr. John P. Hubbard, F.A.C.P., Professor of Public Health and Preventive Medicine, University of Pennsylvania School of Medicine, has been elected President of the Heart Association of Southeastern Pennsylvania.

---

Dr. Horace H. Zinneman, F.A.C.P., has been appointed Associate Professor, Department of Medicine, University of Minnesota Medical School.

Dr. Samuel Bellet, F.A.C.P., Chief of Cardiology at Philadelphia General Hospital, has been awarded \$241,000 by the Department of Health, Education and Welfare, U. S. Public Health Service, for a five-year research program. This grant will be used to seek a critical evaluation of various drugs introduced and used in clinical medicine, with emphasis on cardiovascular diseases.

---

Brigadier General Francis W. Pruitt, F.A.C.P., (MC), U. S. Army, Chief, Department of Medicine, Walter Reed Army Hospital, Washington, D. C., retired from active duty August 31 after thirty years of service. He has accepted a position as Coördinator of Medical Education at Hillcrest Medical Center, Tulsa, Oklahoma.

Colonel Doss O. Lynn, F.A.C.P., (MC), U. S. Army, has been assigned as Chief, Department of Medicine, Walter Reed Army Hospital, succeeding Brigadier General Francis W. Pruitt. For the past two years Colonel Lynn has been Assistant Chief of the Department of Medicine and Chief of the General Medical Service at the same institution.

---

Dr. Donald L. Glenn, F.A.C.P., Philadelphia, Medical Director of the Pennsylvania Railroad, has been named Medical Director of the Stetson Hospital, Philadelphia. Dr. Glenn is a member of President Eisenhower's Committee for the Physically Handicapped.

---

Captain William N. New, F.A.C.P., (MC), U. S. Navy, and Captain Harry A. Weiss, F.A.C.P. (MC), U. S. Navy, have recently reported for duty at the U. S. Naval Hospital, Yokosuka, Japan. Captain New reported as the Commanding Officer and Captain Weiss as the Chief of Medicine. Lieutenant Commander Willis S. Myers, (Associate), (MC), U. S. N., is also on the staff of the Hospital as the Assistant Chief of the Medical Service.

---

Dr. Charles J. Schreader, F.A.C.P., Philadelphia, has been named Professor of Clinical Medicine at Woman's Medical College of Pennsylvania.

---

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, and Dr. Theodore G. Klumpp, F.A.C.P., New York, were guest speakers at the 10th biennial Rocky Mountain Medical Conference in Denver, Colorado.

---

Major General Elbert DeCoursey, F.A.C.P., Commandant of the Army Medical Service School, has retired at Brooke Army Medical Center after more than thirty-one years of service. Dr. DeCoursey will become Director of the Southwest Foundation for Research and Education, and Director of Scientific Research at Trinity University, San Antonio, Texas, as a full Professor. Dr. DeCoursey is one of the group of eminent American scientists who have been studying the biologic effects of nuclear radiation since the first atomic bombs were dropped on Japan in 1945.

---

Dr. Mildred C. J. Pfeiffer, F.A.C.P., Philadelphia, was introductory speaker at the 8th Annual Health Conference, State College, Pa., August 17-20, 1959.

Dr. John W. Ferree, F.A.C.P., New York, has assumed the post of Executive Director of the National Society for the Prevention of Blindness.

---

Drs. Simon Rodbard, Buffalo, Sumner S. Cohen, Minneapolis, and David W. Kramer, Philadelphia, all Fellows of the College, were guest speakers at the 27th Annual Assembly of the Omaha Mid-West Clinical Society in Omaha, November 2-5, 1959.

---

Dr. Russell M. Wilder, M.A.C.P., and Emeritus member of the staff of the Mayo Clinic, has been named an Honorary Member of the American Dietetic Association.

---

Dr. E. Gordon Margolin, (Associate), has been appointed as full-time Director of the Department of Internal Medicine and Chairman of the Medical Staff, Committee on Education, of the Jewish Hospital of Cincinnati. He is also Assistant Professor of Clinical Medicine at the University of Cincinnati College of Medicine.

---

Colonel Fred H. Mowrey, F.A.C.P., (MC), Chief of Professional Services and former Chief, Department of Medicine, Letterman Army Hospital, San Francisco, retired from active duty on July 31. He will assume new office as Assistant Medical Director (Chief, Medical Service) of the Los Angeles County General Hospital, where he served his internship.

---

Dr. Myron E. Freedman, (Associate), Hartford, has been appointed Director of Medical Education, McCook Hospital.

---

Dr. Reginald C. Edson, F.A.C.P., West Hartford, Conn., has been elected President of the Connecticut Trudeau Society.

---

Dr. Edward Martin, F.A.C.P., New Britain, Conn., has recently been elected a Fellow of the International Society of Hematology.

---

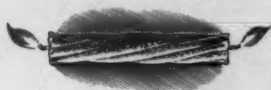
Dr. Harold J. Lehmus, F.A.C.P., Manchester, Conn., has been reelected President of the Manchester Heart Association.

---

Dr. Stewart P. Seigle, F.A.C.P., Hartford, has been elected President-Elect of the American Society of Internal Medicine.

---

Dr. John C. Leonard, F.A.C.P., College Governor for Connecticut, has been elected President of the Yale Association of Alumni in Medicine.



For the patient  
whose vagus  
burns at  
both ends—  
**Pro-Banthine®**  
with **Dartal®**

- eases psychic stress
- controls enteric distress in  
gastrointestinal spasm

When tensions smolder and set off associated hyperactivity in the gastrointestinal tract, the patient needs relief at both ends of the vagus.

In such cases, Pro-Banthine with Dartal eases the psychic stress and moderates the excess gastrointestinal spasm and hypermotility. Pro-Banthine acts selectively to calm the vagal overactivity in the stomach and intestines. Dartal acts speedily and safely to dampen psychic pressures.

Combined as Pro-Banthine with Dartal, these two drugs provide a highly useful agent for moderating both mood and motility in patients suffering from gastrointestinal spasm.

Pro-Banthine with Dartal contains 15 mg. of Pro-Banthine (brand of propantheline bromide) and 5 mg. of Dartal (brand of thiopropazate dihydrochloride) in each tablet.

**Dosage:** One tablet three times daily.

G. D. Searle & Co., Chicago 80, Illinois.  
Research in the Service of Medicine.



## CONGESTIVE FAILURE

"Chlorothiazide appears to represent a significant advance in the treatment of patients with congestive heart failure . . . ; its decided advantages are (1) effective oral administration, (2) apparent lack of toxicity, (3) high patient acceptance, (4) sustained diuretic action . . ."

Keyes, J.W. and Berlacher, F.J.: J.A.M.A. 188:109, (Jan. 10) 1959.

Dosage: One or two 500 mg. tablets DIURIL once or twice a day.

# DIURIL<sup>®</sup>

CHLOROTHIAZIDE

a continuing  
and consistently  
outstanding record  
of safety and  
efficacy in:

Supplied: 250 mg. and 500 mg. scored tablets DIURIL (Chlorothiazide). DIURIL is a trademark of Merck & Co., Inc. Additional information is available to the physician on request.



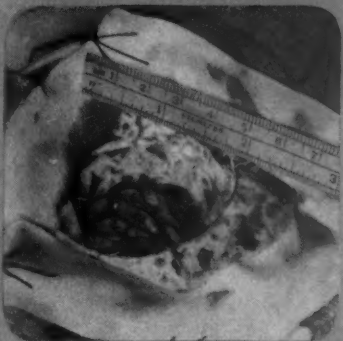
MERCK SHARP & DOHME  
Division of Merck & Co., Inc., Philadelphia 1, Pa.

©1959 Merck & Co., Inc.



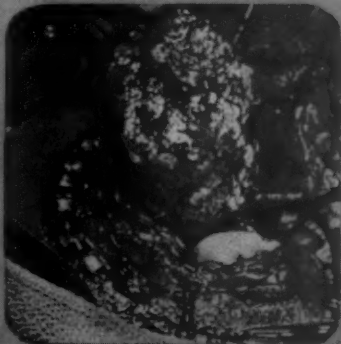
a new  
sound-  
color  
film...

"A new approach  
to the reduction  
of intracranial  
pressure with  
Urea-Invert  
sugar"



# UREVERT™

(LYOPHILIZED UREA  
AND TRAVERT®)



TRAVENOL LABORATORIES, INC.

pharmaceutical products division of

BAXTER LABORATORIES, INC.

Morton Grove, Illinois

The clinical data presented in the film are taken from the case histories of more than 550 patients who received urea-invert sugar solution (UREVERT™) at the University of Wisconsin hospitals for a variety of cranial disorders.

The use of Urevert to facilitate intracranial surgery in glioblastoma multiforme, optic nerve glioma, fronto-temporal meningioma, cerebellar astrocytoma and retrogasserian rhizotomy is illustrated.

A comparison of Urevert with other hypertonic solutions demonstrates its superiority to such agents in reducing cerebrospinal fluid pressure and brain volume.

For Your Group—showing of this 19 minute film may be arranged by writing to Medical Film Library, Travenol Laboratories, Inc., Morton Grove, Illinois.

now...ulcer  
patients  
sleep  
through  
the night  
without  
pain or  
discomfort

new **TRAL<sup>®</sup> 75<sup>mg</sup>** Gradumet<sup>®</sup>

(Hexocyclium Methylsulfate in Long-Release Dose Form\*, Abbott)

new anticholinergic dosage form aimed specifically at controlling nocturnal secretion

new ataractic-anticholinergic combination for  
medical management of functional bowel disease

# new **TRALCYON**<sup>TM</sup>

FILMTAB

(Hexocyclium Methylsulfate with Ectylurea, Abbott)

combining a highly selective anticholinergic  
with one of the most subtle and safe calmatives

New TRALCYON (Filmtab) is indicated for the management of gastrointestinal disorders characterized by increased motility of the colon. Disorders such as spastic and irritable colon, constipation, hyperreflexia of the stomach or intestines and anxiety disorders with vague gastrointestinal complaints respond well to treatment with Filmtab TRALCYON. When psychological factors contribute to established colonic lesion such as spastic ileus, chronic constipation, biliary colic, etc., TRALCYON will usually produce greater benefit by administration of an ataractic-anticholinergic agent. Filmtab TRALCYON tablets (U.S. Pat. 3,663,851), each containing Tralcyon 10 mg., with ectylurea, 500 mg., are available in pharmacies in bottles of 30 and 60.

Trade name of Filmtab is registered in the U.S. Patent Office. © 1970, Abbott Laboratories, Abbott Park, Illinois.



## SUSAN, THE TECHNICIAN TELLS HOW:

"Patrician's comfort  
and simplicity  
please everyone"

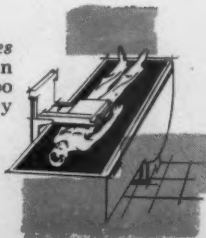
"Our radiologist likes  
the *Patrician* for flu-  
oroscopy. Traded his  
old unit... got rid of  
tiresome tussles with  
an awkward fluoro-  
scopic screen."



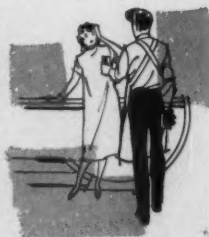
"Poor Mrs. Smith had  
tremors — no prob-  
lem for me, though.  
The *Patrician* '200'  
is built for split-sec-  
ond radiography that  
really 'stops' motion."



"Tall Johnny stretches  
comfortably. Even  
6½ footers are not too  
big for this roomy  
81" table."



"Miss Jones says  
she 'feels faint' —  
I'm glad to know  
the *Patrician* han-  
dles easily. Switch-  
es quickly from  
fluoroscopy to ra-  
diography... min-  
imizes examina-  
tion time for high-  
strung patients."



- Ask your G-E x-ray representative for full details on *Patrician's* big-table convenience. Or clip this coupon for a copy of new illustrated catalog.

**GENERAL  ELECTRIC**

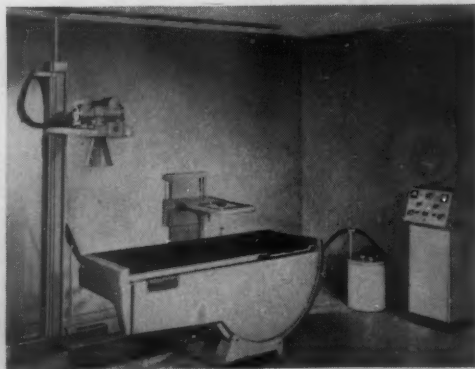
**X-RAY DEPARTMENT  
GENERAL ELECTRIC CO.  
Milwaukee 1, Wisconsin, Rm. M-111**

Please send me:

- ☐ New 8-page **PATRICIAN** bulletin
- ☐ Facts about deferred payment
- ☐ **MAXISERVICE**® all-inclusive rental plan

Name.....

Address.....



Why Levophed is "...the preferred form of therapy..." in

# coronary shock

most potent<sup>2,3</sup>

fastest acting<sup>4</sup>

controllable action<sup>1,5</sup>

saves more lives<sup>6</sup>

# Levophed<sup>®</sup>

bitartrate

With the prompt use of Levophed, 28 per cent of patients who would have died of severe coronary shock now live.<sup>6</sup>

*natural antishock  
pressor hormone*

#### References:

1. Shock in myocardial infarction, *Heart Bull.* 6:107, Nov.-Dec., 1957.
2. Agress, C. M.: *Am. J. Cardiol.* 1:231, Feb., 1958.
3. Garal, Oliver, and Smith, K. S.: *Brit. M. J.* 1:247, Feb. 1, 1958.
4. Agress, C. M., and Binder, M. J.: *Am. Heart J.* 54:458, Sept., 1957.
5. Corday, Eliot: Paper read at meeting of the College of Physicians, Atlantic City, N. J., April 28-May 2, 1958.
6. Tainter, M. L.: *Bol. Asoc. med. Puerto Rico* 47:305, Aug., 1955.

*Winthrop*  
LABORATORIES  
New York 20, N. Y.

LEVOPHED (BRAND OF LEVATERENOL)  
TRADEMARK REG. U. S. PAT. OFF.

# for F.A.C.P.'s only . . . .

Holidays . . Birthdays . . Anniversaries . . .

Or just anytime



## FELLOWSHIP INSIGNIA FOR ACADEMIC GOWN

The insignia for academic dress consist of a cross in the shape of the Fellowship Key, exact size as illustrated, of green velvet with the Seal of the College outlined in solid gold braid, to be worn at the option of the Fellow on the right sleeve of the academic gown, about three inches below the shoulder seam. These insignia are made up on order ready to be stitched to the gown.

*Price, delivered, \$7.00.*

## FELLOWSHIP TIE CLASP



This distinctive tie clasp meets the need of those who have no use for a Fellowship Key because they do not wear a watch chain. The College emblem is wrought in solid gold; the bar is gold filled in good and lasting quality.

*Price, including tax, delivered, \$12.00.*



## FELLOWSHIP KEY

This beautifully and expertly designed charm, bearing the Seal of the College, is wrought in 10K solid gold and embossed in the College colors. Shown actual size. Initials of Fellow and date of election engraved on the back at no extra charge.

*Price, including tax, delivered, \$12.00.*

*Available also, in smaller size, as a Fraternity Pin with Safety Catch, \$5.00.*

The American College of Physicians  
4200 Pine Street, Philadelphia 4, Pa.

Date . . . . .

Dear Sir:

Please send me:

..... Fellowship Insignia for Academic Gown .....	\$ 7.00 .....	\$ .....
..... Fellowship Key .....	12.00 .....	\$ .....
..... Fellowship Pin .....	5.00 .....	\$ .....
..... Fellowship Tie Clasp .....	12.00 .....	\$ .....

My check for \$..... is enclosed. Total .....

Name (Please Print) .....

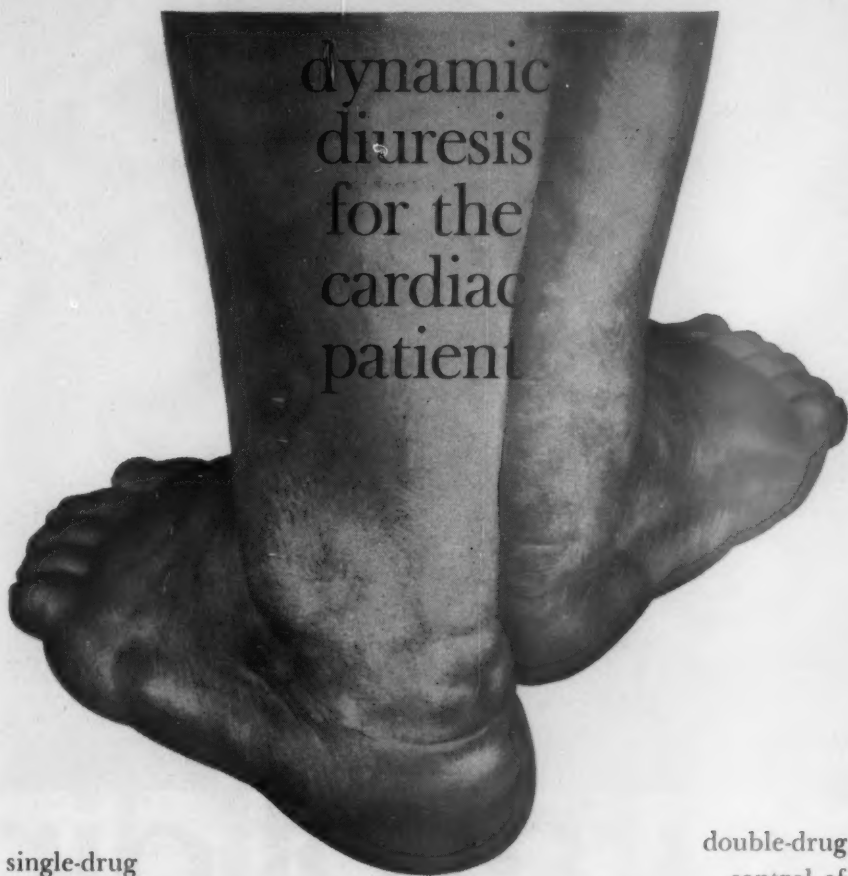
Street .....

City .....

Zone .....

State .....

Please Mention this Journal when writing to Advertisers



dynamic  
diuresis  
for the  
cardiac  
patient

single-drug  
control of  
cardiac edema

DIAMOX mobilizes bicarbonate and with it sodium, and the fluids of edema...reduces water retention with no notable changes in blood pressure or electrolyte balance. One tasteless tablet each morning...easy to take...rapidly excreted...does not interfere with sleep.

double-drug  
control of  
congestive heart failure


DIAMOX alternated with chloride-regulating agents provides more dynamic diuresis than can any used alone...helps potentiate diuretic effect and counterbalance the tendency toward systemic alkalosis of chlorothiazide and mercurials...lessens risk of drug tolerance...extends intensive diuretic therapy.

Supplied: Scored tablets of 250 mg., and Vials of 500 mg. for parenteral use.

# DIAMOX<sup>®</sup>

Acetazolamide Lederle

HCO<sub>3</sub><sup>-</sup> regulating diuretic

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York 

Please Mention this Journal when writing to Advertisers



in arthritis

# Butazolidin

(phenylbutazone ester)

tablets • alka capsules

potent • nonhormonal • anti-inflammatory agent

**BUTAZOLIDIN** tablets or the Alka capsules are equally effective but individually adaptable in a wide range of arthritic disorders.

Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

**Gouty Arthritis:** "...95 per cent of patients experienced a satisfactory response..."

**Rheumatoid Arthritis:** In "A total of 215 cases...over half, 50.7 per cent showed at least major improvement,

with 21.8 per cent showing minor improvement..." **Osteoarthritis:** 301 cases showed "...a total of 44.5 per cent with complete remission or major improvement. Of the remainder, 28.2 per cent showed minor improvement..." **Spondylitis:** All patients "...experienced initial major improvement that was maintained throughout the period of medication." **Painful Shoulder Syndrome:** Response of 70 patients with various forms showed "...8.6 per cent complete remissions, 47.1 per cent major improvement, 20.0 per cent minor improvement..."

**References:** 1. Graham, W.: *Canad. M. A. J.* 79:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: *Am. Pract. Digest Treat.* 8:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E., and Champlin, B. M.: *New England J. Med.* 256:368, 1957. **Availability BUTAZOLIDIN®** (phenylbutazone ester): Red coated tablets of 100 mg. BUTAZOLIDIN® Alka: Capsules containing BUTAZOLIDIN® (phenylbutazone ester), 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide, 1.25 mg.

**geigy**  
ARDSLEY, NEW YORK

“SAFE AND EFFECTIVE MAINTENANCE THERAPY...HAD BEEN A PROBLEM AT OUR INSTITUTION UNTIL WE USED GITALIN [GITALIGIN]...”\*

*Arteriosclerotic Heart Disease*

WIDEST SAFETY MARGIN—AVERAGE THERAPEUTIC DOSE IS ONLY  $\frac{1}{8}$  THE TOXIC DOSE.†

FASTER RATE OF ELIMINATION THAN DIGITOXIN OR DIGITALIS LEAF.

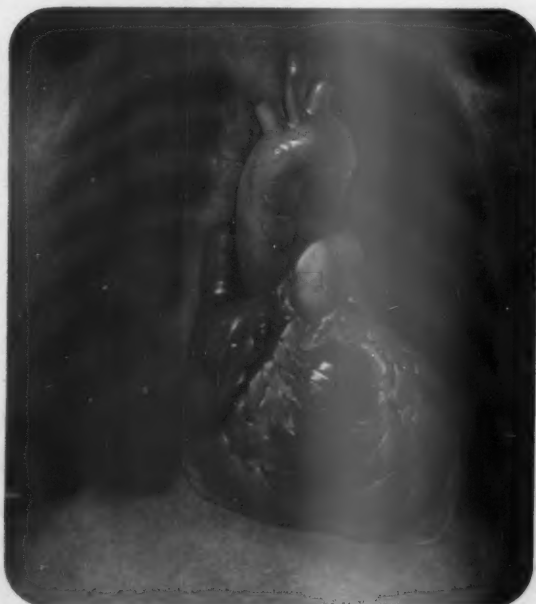
THESE SIMPLE DOSAGE EQUIVALENTS MAKE IT EASY TO SWITCH YOUR PATIENT TO GITALIGIN—0.5 mg. of Gitaligin is approximately equivalent to 0.1 Gm. digitalis leaf, 0.5 mg. digoxin or 0.1 mg. digitoxin.

**Supplied:**

GITALIGIN 0.5 mg. Tablets—bottles of 30 and 100.

GITALIGIN Injection Ampuls—2.5 mg. in 5 cc. sterile, I. V. solution.

GITALIGIN Drops 30 cc. bottle with special calibrated dropper.



# GITALIGIN<sup>®†</sup>

WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

\*HARRIS R., AND DEL GIACCO R. R.: AM. HEART J. 52:300, 1956 • †WHITE'S BRAND OF AMORPHOUS GITALIN • ‡BIBLIOGRAPHY ON REQUEST

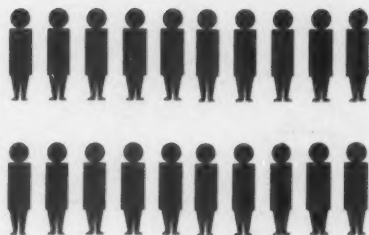
# FOR UNMATCHED TOLERANCE AND OPTIMAL ABSORPTION

## MOL-IRON VITAMIN C

(Molybdenized-Ferrous Complex)

IN IRON DEFICIENCY ANEMIA—SPECIALLY WHEN IRON ABSORPTION IS DEFECTIVE

MOL-IRON...  
WELL TOLERATED  
by **97.9%**  
of 336 patients<sup>1-9</sup>



But 22.4%  
G. I. side  
effects  
with  
FeSO<sub>4</sub>

**VITAMIN C**—"Optimal absorption of iron is best assured by  
administering it in the ferrous form with ascorbic acid..."<sup>10</sup>

**MOL-  
IRON**

WITH  
**VITAMIN  
C**  
TABLETS

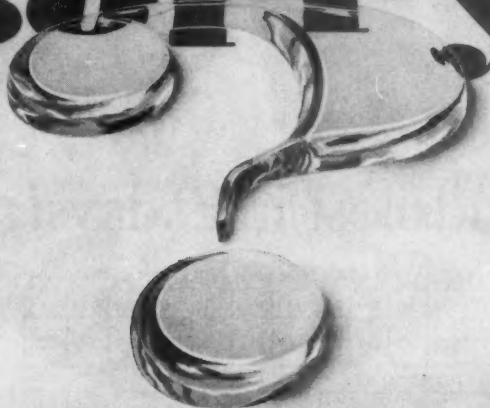
Each contains—Mol-Iron (ferrous sulfate 195 mg., and molybdenum oxide 3 mg.) plus ascorbic acid 75 mg. Bottles of 100. Dose—1 or 2 tablets t.i.d.

1. Brit. M. J. 1:407, 1952. 2. Bull. Margaret Hague Mat. Hosp. 1:66, 1948. 3. Am. J. Obst. & Gyn. 57:541, 1949. 4. Connecticut M.J. 14:930, 1950. 5. J. Lancet 66:218, 1946. 6. Am. J. Obst. & Gyn. 62:947, 1951. 7. Am. J. Med. Sc. 212:76, 1946. 8. Obst. & Gynec. 5:201, 1955. 9. J. Ped. 41:170, 1952. 10. Ann. Int. Med. 42:458, 1955.

*White's*

WHITE LABORATORIES, INC.  
KENILWORTH, NEW JERSEY

# better safe than sorry



No doubt about it. It is better to be safe than sorry. And when you prescribe **Mysteclin-V**, you are playing safe. **Mysteclin-V** — a combined broad spectrum antibiotic/antifungal agent is specially designed to combat most of the commonly encountered pathogenic organisms<sup>1</sup> and, simultaneously, to protect against fungal superinfections.<sup>2,3</sup> With the increased use of broad spectrum antibiotics the incidence of such superinfections has risen and the danger of superinfection is especially great in pregnant patients, in diabetics, and in those who require long courses of antibiotic therapy.

**Mysteclin-V controls infection and prevents superinfection** — with the proved effectiveness of tetracycline phosphate complex and Mycostatin, the first safe antifungal antibiotic. Thousands of successfully treated cases<sup>4-6</sup> of respiratory, urinary tract, intestinal, and miscellaneous infections attest to the safety and clinical effectiveness of **Mysteclin-V**. When you prescribe **Mysteclin-V**, you make a telling assault on bacterial infection and prevent fungi from gaining a foothold.

**Supplied:** Capsules (250 mg./250,000 u.), bottles of 16 and 100/Half-strength Capsules (125 mg./125,000 u.), bottles of 16 and 100/Suspension (125 mg./125,000 u. per 5 cc.), 2 oz. bottles/Pediatric Drops (100 mg./100,000 u. per cc.), 10 cc. dropper bottles.

"MYSTECLIN", "SUNYCH", and "MYCOSTATIN" are SQUIBB TRADEMARKS

**References:** 1. Cronk, G.A.; Naumann, D.E. and Casson, K.: *Antibiotics Annual 1957-1958*, New York, Medical Encyclopedia Inc., 1958, p. 197. 2. Childs, A.J.: *Brit. M.J.* 1:660 (Mar.) 1956. 3. Newcomer, V.D.; Wright, E.T., and Sternberg, T.H.: *Antibiotics Annual 1954-1955*, New York, Medical Encyclopedia Inc., 1955, p. 686. 4. Gimble, A.I.; Shea, J.G., and Katz, S.: *Antibiotics Annual 1955-1956*, New York, Medical Encyclopedia Inc., 1956, p. 676. 5. Stone, M.L., and Mersheimer, W.L.: *Antibiotics Annual 1955-1956*, New York, Medical Encyclopedia Inc., 1956, p. 862. 6. Campbell, E.A.; Prigot, A., and Dorsey, G.M.: *Antibiotic Med. & Clin. Ther.* 4:817 (Dec.) 1957.

## Mysteclin-V

SQUIBB TETRACYCLINE PHOSPHATE COMPLEX (SUNYCH) AND NYSTATIN (MYCOSTATIN)



**SQUIBB**  
Squibb Quality —  
the Priceless Ingredient

Please Mention this Journal when writing to Advertisers



Before Esidrix:  
Weight 176 lbs.

## 27 pounds lost in 19 days; ascites and

RECORD OF TREATMENT (At a leading New York City hospital. Photos used with permission of the patient.)

Date	3/3	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13	3/14	3/15	3/16	3/17	3/18	3/19	3/20	3/21	3/22	3/23
Weight (pounds)	178	176	170	169	167	159	158	158	157	153	155	155	156	154	153	154	153	—	—	151	149
Rx	M* Esidrix 50 mg. b.i.d.																				

\*Mercurial diuretic



# Esidrix<sup>T.M.</sup>

(hydrochlorothiazide CIBA)

pre-eminently effective whenever diuresis is desired

*Indicated in: congestive heart failure . . . nephrosis and nephritis . . . toxemia of pregnancy . . . premenstrual edema . . . edema of pregnancy . . . steroid-induced edema . . . edema of obesity*

*Supplied: Esidrix Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored); bottles of 100 and 1000.*

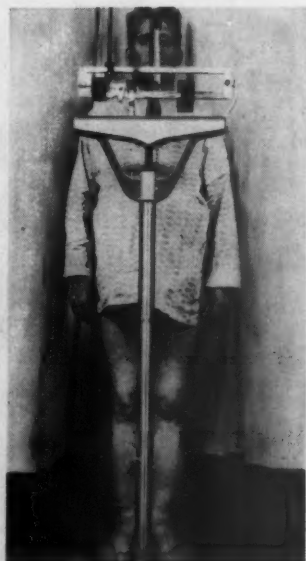


After 19 days on Esidrix:  
Weight 149 lbs.



## pedal edema reduced with Esidrix

H. K., 44 years old, was admitted to the hospital on 3/3/59 with complaints of *swollen abdomen, swelling of both legs and exertional dyspnea*. These symptoms had been intensifying over a three-week period. The patient's history included heavy drinking since the age of 18, and one prior admission to the hospital in 1954 with ascites and pedal edema. Diagnosis, at that time, was Laennec's cirrhosis, and the patient responded well to a regimen of diuretics, salt restriction and multivitamins. There was no recurrence up to that leading to his current admission.



*Clinical findings worthy of note:*  
Eyes — conjunctivae and sclerae slightly icteric. Chest — diaphragm elevated. Abdomen — girth enlarged, definite fluid wave. Liver palpated 4 fingerbreadths below the costal margin; no other palpable viscera. Extremities — pedal edema (4+).

The patient is well developed and not in acute distress. Blood pressure, 140/80 mm. Hg; pulse, 112/min.; respiration, 20/min. Impression: Laennec's cirrhosis — decompensated.

*Treatment:* Mercurial diuretic on 3/3 and 3/4, followed by Esidrix, 50 mg. b.i.d., from 3/5 to 3/23 when patient signed out of hospital. Esidrix induced copious diuresis resulting in almost complete disappearance of edema.

stop as well as prevent  
nausea and vomiting

# NEW Tigan

now in oral,  
parenteral, and  
suppository forms

*effective but not  
"side effective"*

Tigan blocks emetic impulses at the chemoreceptor trigger zone (CTZ),<sup>1</sup> a medullary structure activating the vomiting center. While Tigan shares with the phenothiazines the mode of antiemetic action, this is their only similarity.<sup>1</sup> In extensive clinical studies<sup>2-14</sup> Tigan, unsurpassed in specificity, has exhibited a virtually complete absence of side effects. Tigan has demonstrated no sedative or tranquilizing properties, no hypotensive or supramedullary effects, no extrapyramidal tract stimulation or hepatic toxicity.<sup>2-14</sup>



Please Mention this Journal when writing to Advertisers

## no special precautions— no known contraindications

*in nausea/vomiting  
of gastrointestinal  
disorders*

Complete or moderate relief in 78 per cent of acute or chronic gastroenteritis patients;<sup>13</sup> "We did not find a single toxic reaction . . . no side effects, such as sedation, skin rash . . . no changes in pulse, respiration, or . . . blood pressure."<sup>13</sup>

*in nausea/vomiting  
of pregnancy*

No evidence of sedation or other side effects<sup>12</sup> observed in a series of patients of whom 94 per cent became asymptomatic on Tigan. On other antiemetic medication, several had failed to respond or had complained of drowsiness.<sup>12</sup>

*in nausea/vomiting  
of radiation sickness*

Protected with Tigan " . . . not one patient had to discontinue [deep radiation] treatments. . . ."<sup>5</sup>

*in nausea/vomiting  
of drug  
administration*

" . . . large intermittent dose[s] of [nitrogen mustard and other drug] therapy could be given without the associated nausea and vomiting that we had seen before."<sup>7</sup>

# Tigan

*specific  
antiemetic  
antinauseant*

*no sedative properties  
no tranquilizer side effects*

**Suggested uses:** Both prophylactic and therapeutic control of nausea and vomiting associated with pregnancy, travel sickness, gastrointestinal disorders, operative procedures, carcinomatoses, toxicoses, other underlying disease processes, drug administration and radiation therapy.

**Dosage:** Adults—1 or 2 capsules, orally, 2 cc intramuscularly, q.i.d. or 1 suppository, q.i.d. For children's dosage, consult literature.

**In nausea and vomiting of pregnancy**—Satisfactory control is usually achieved with an initial dose of two capsules immediately upon awakening. If possible, the patient should remain in bed for one-half to one hour following this dose. When nausea and vomiting are not confined to the morning hours, supplemental doses of one or two capsules should be given throughout the day at intervals of three to four hours.

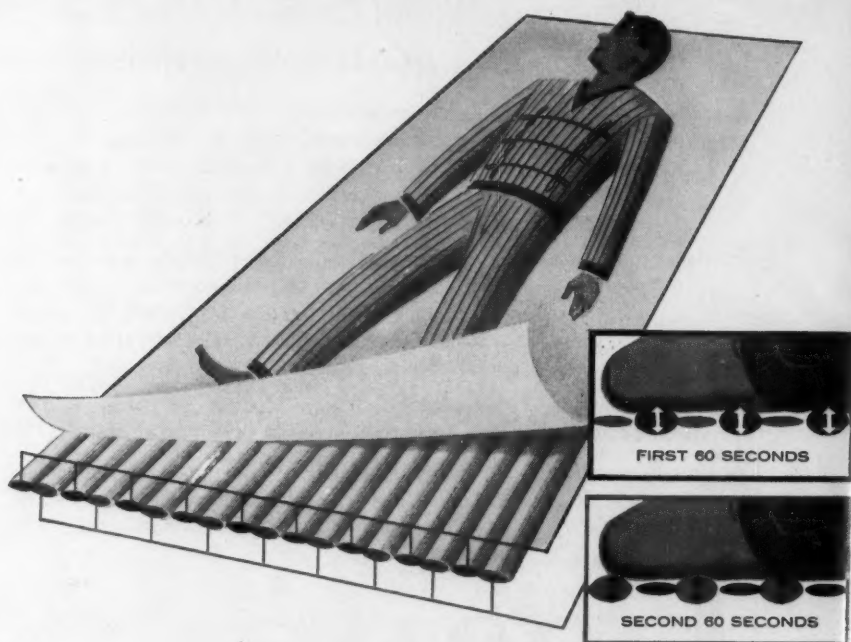
**How Supplied:** Tigan capsules, 100 mg, blue and white—bottles of 100 and 500. Tigan ampuls, 2 cc (100 mg/cc)—boxes of 6 and 25. Tigan Pediatric Suppositories, 200 mg, boxes of 6 and 25.

**References:** 1. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, in press. 2. W. B. Abrams, I. Roseff, J. Kaufman, L. Goldman and A. Bernstein, to be published. 3. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.*, 9:109, 1958. 4. O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 5. J. A. Lucinian *ibid* 6. D. W. Molander, *ibid*. 7. B. I. Shmder, *ibid*. 8. W. S. Derrick *ibid*. 9. B. Wolfson and F. F. Foldes, *ibid* 10. L. McLaughlin, *ibid*. 11. Reports on file, Roche Laboratories. 12. Personal communications. 13. W. K. Gauthier, Discussant at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 14. H. E. Davis, *ibid*.

TIGAN<sup>TM</sup>. Hydrochloride-  
4-(2-dimethylaminoethoxy)-  
N-(3,4,5-trimethoxybenzoyl)-  
benzylamine hydrochloride  
ROCHE®

**ROCHE**   
**LABORATORIES**  
Division of  
Hoffmann-La Roche Inc.  
Nutley 10, N. J.

Please Mention this Journal when writing to Advertisers



### Tired of Fighting the Bedsores Problem?

#### *APP Units Are the Proved Way to Help Cure and Prevent Decubiti*

The Alternating Pressure Pad helps prevent and cure decubiti by automatically shifting body pressure points every two minutes as illustrated . . . thus maintaining adequate circulation and preventing tissue breakdown. The combination of an APP Unit and normal nursing care starts granulation usually within a few days.

Equally important, APP Units eliminate the constant turning of patients, (which in some cases adversely affects recovery) and provide passive massage on a 24-hour basis.

Thousands of APP Units are now in use. Many more are needed for private patients in hospitals and nursing homes. Units are available from leading surgical supply houses for standard beds, respirators and wheel chairs.

APP Units are manufactured solely by Air Mass, Inc., Cleveland, Ohio, U. S. A.



#### MAIL THIS COUPON FOR ACTION

THE R. D. GRANT COMPANY

805E Hippodrome Building  
Cleveland 14, Ohio, U. S. A.

- ☐ Please send complete details on APP Units.
- ☐ Please send APP Unit Clinical Reports.
- ☐ Please have your representative call me to arrange a demonstration.

Institution \_\_\_\_\_

Street \_\_\_\_\_

City \_\_\_\_\_ Zone \_\_\_\_\_ State \_\_\_\_\_

Requested by \_\_\_\_\_

Please Mention this Journal when writing to Advertisers



## THE HOUSE-CALL ANTIBIOTIC

*Reassuring wide range of action when culture and sensitivity tests are impractical  
Effectiveness demonstrated by its use in more than 6,000,000 patients  
since introduction of original product (Signemycin®)*

# COSA-SIGNEMYCIN®

*glucosamine-potentiated tetracycline  
with triacetyloleandomycin*

*Capsules*  
125 mg., 250 mg.

*Oral Suspension*  
raspberry flavored, 2 oz. bottle, 125 mg.  
per teaspoonful (5 cc.)

*Pediatric Drops*  
raspberry flavored, 10 cc. bottle (with calibrated  
dropper), 5 mg. per drop (100 mg. per cc.)

*Bibliography and professional information booklet  
COSA-SIGNEMYCIN available on request.*

**Pfizer** *Science for the world's well-being™*

**Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.**

## In prophylaxis of angina pectoris

### "The best results..."

"The best results... in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE]. . . ." Russek<sup>1</sup> so reported using double-blind methods in an important new study of pentaerythritol tetranitrate, a placebo, meprobamate, and EQUANITRATE. EQUANITRATE reduces the frequency and severity of attacks and controls angina-triggering emotions.

Supplied: EQUANITRATE 10 (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. EQUANITRATE 20 (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

1. Russek, H.I.: Am. J. Cardiol. 3:547 (April) 1959.

# Equanitrate\*

Meprobamate and Pentaerythritol Tetranitrate, Wyeth

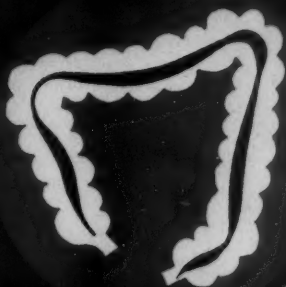


Philadelphia 1, Pa.



NEWLY AVAILABLE  
EQUANITRATE 20

\*Trademark



- Prompt remission of symptoms
- Bleeding and frequency of stools sharply reduced
- Healing of rectal mucosa within a month in most cases
- Can be given safely over long periods of time

# Azulfidine®

BRAND OF SALICYLAZOSULFAPYRIDINE

*the most  
valuable drug  
in the  
treatment of*

**Ulcerative  
Colitis**

"The most widely accepted sulfonamide preparation today for the therapy of chronic ulcerative colitis is salicylazosulfapyridine (Azulfidine)."

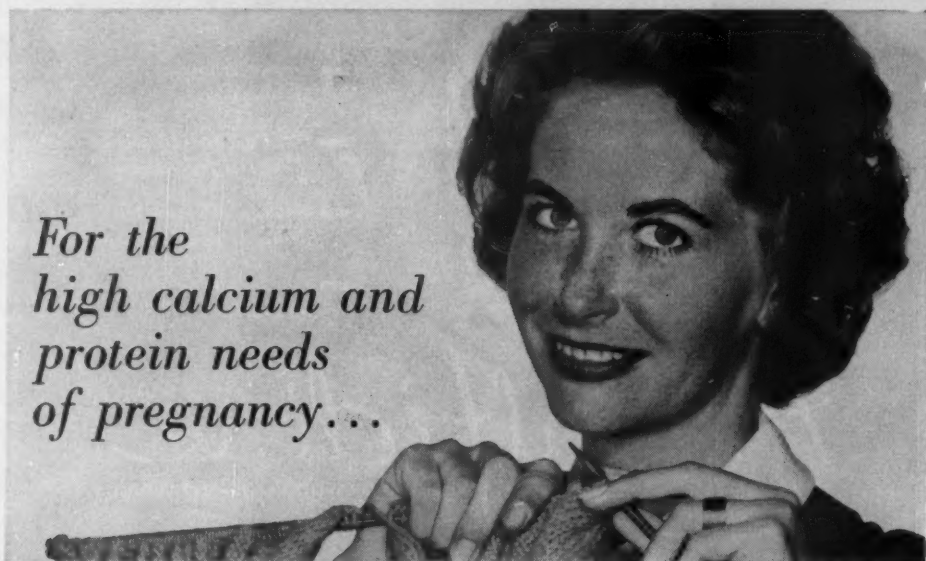
Hightower, N.C., Jr., and others:  
*Am. J. Digest. Dis.* 3:931 (Dec.) 1958

*Also valuable in treatment of regional enteritis and other forms of colitis*

*Pharmacia Laboratories, Inc.*

New York City.

*For the  
high calcium and  
protein needs  
of pregnancy...*



## New *self-enriched* Carnation Instant

25% more protein, calcium, B-vitamins,  
richer flavor than ordinary nonfat milk

New Carnation Instant can give your patients a *more delicious* nonfat milk—*extra-rich* in natural milk calcium, protein and B-vitamins. This new fresh flavor crystal-form nonfat milk can be *self-enriched*. The patient simply adds one extra spoonful of crystals per 8-oz. glass when mixing—to gain 25% more calcium, protein and B-vitamins than ordinary nonfat

milk—and far richer flavor. Convenience and low cost also encourage acceptance. Calorie count remains low (400 per quart), facilitating weight control.

In examining the chart, physicians will recognize the particular value of the increase in natural milk calcium, more effectively utilized than most medicinal calcium salts.

	Calcium	Protein	Riboflavin	Thiamine
National Research Council Recommended Daily Dietary Allowances During Second Half of Pregnancy	1.5 Grams	78.0 Grams	2.0 Mg.	1.3 Mg.
Amount and Percent of Daily Dietary Allowances Provided by 1 Quart of 25% self-enriched Carnation Instant	1.48 Grams (98%)	41.3 Grams (53%)	2.26 Mg. (113%)	.40 Mg. (30%)

### 25% self-enriched Carnation Instant

Simply add 1 tablespoon extra Carnation Instant per glass, or 1/3 cup extra Carnation Instant per quart, over regular package directions.



*in India, it's called 'Delhi belly'*



*diarrhea by any name*

GASTROENTERITIS

BACILLARY DYSENTERY

PARADYSENTERY

SALMONELLOSIS

DIARRHEA OF THE NEWBORN

NONSPECIFIC DIARRHEA

"SUMMER COMPLAINT"

*usually responds rapidly to*

# Cremomycin<sup>®</sup>

NEOMYCIN-SULFASUXIDINE<sub>®</sub>-KAOLIN-PECTIN SUSPENSION

*for rapid relief of virtually all diarrheas*

*fruit-flavored, readily accepted by patients of all ages\**

Neomycin — rapidly bactericidal against most intestinal pathogens, but is relatively ineffective against such diarrhea-causing organisms as *Shigella*.

SULFASUXIDINE<sup>®</sup> — an ideal adjunct to neomycin because it is highly effective against *Shigella* and certain other neomycin-resistant organisms.

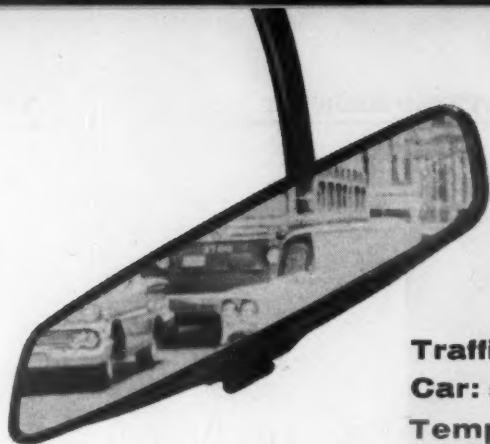
Kaolin and Pectin — coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

\*For infants, CREMOMYCIN may be administered in the regular bottle feeding since its fine particles easily pass through a standard nursing nipple.



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILA. 1, PA.

CREMOMYCIN AND SULFASUXIDINE (SUCCINYL-SULFATHIAZOLE) ARE TRADEMARKS OF MERCK & CO., INC.



**Traffic: jammed,**

**Car: stalled**

**Temper: mild**

**Ulcer: quiet**

Here's a man whose ulcer once would have protested strongly—not just at traffic problems—but at the entire gamut of stress to which modern man is subjected.

His physician, aware that *the patient as well as the ulcer* must be treated, has prescribed ALUDROX SA.

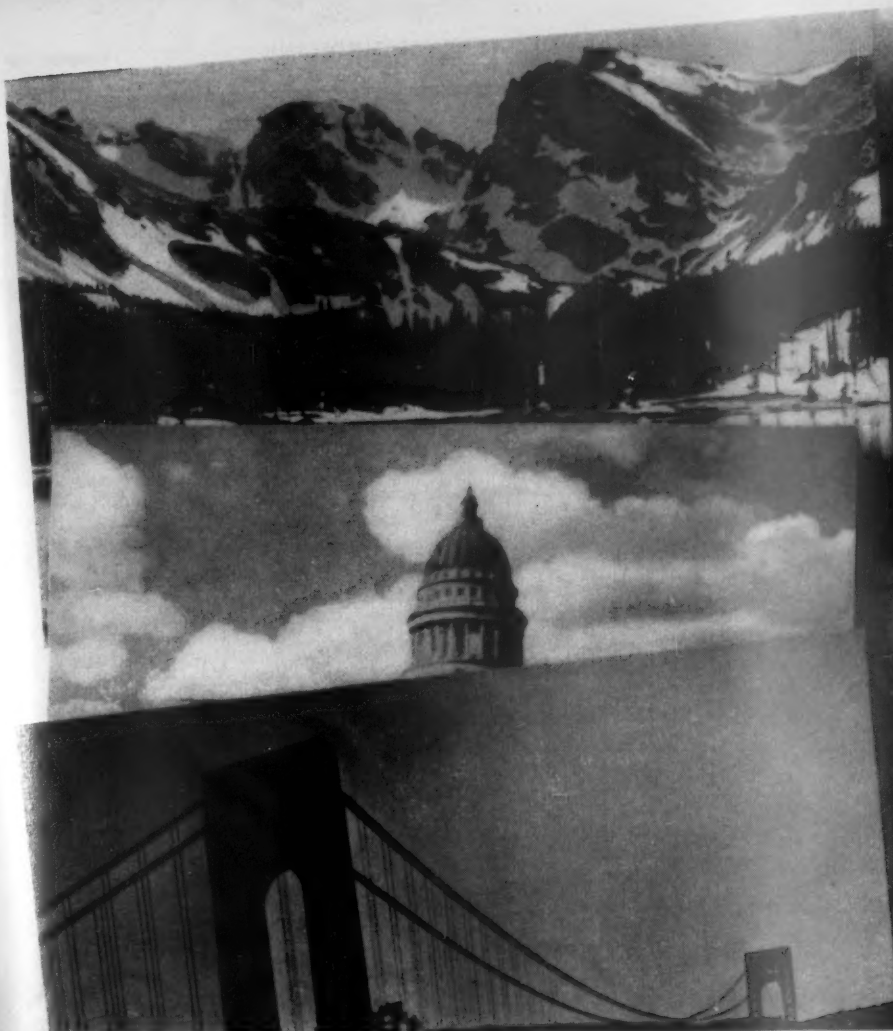
eases tension • promotes healing  
relieves pain • reduces acid  
secretion • inhibits gastric motility

## ALUDROX<sup>®</sup> SA

Suspension and Tablets: Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide and Butabarbital, Wyeth



Philadelphia 1, Pa.



Polaramine — the closest to a perfect antihistamine — offers four major benefits to provide your patients with greater freedom from seasonal and nonseasonal allergies.

*Greater therapeutic response ... daylong or nightlong relief with a single 4 mg. Polaramine Repetab. Greater protection at lower dosages than with other antihistamines. Greater safety... highest therapeutic index (3380) of all antihistamines. Greater freedom from side effects. 4 mg. Polaramine Repetabs in bottles of 100 and 1000.*

POLARAMINE® Maleate, brand of dextro-chlorpheniramine maleate.  
REPETABS®, Repeat Action Tablets.

EN-1487-9

SYMBOL OF THE  
ONE-DOSE  
CONVENIENCE  
YOU WANT FOR  
YOUR PATIENT



*Wherever  
the 4 winds  
blow...  
new 4 mg.*

## **POLARAMINE REPETABS**

for relief of allergic reactions  
and day-to-day maintenance

*Schering*

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

## TO REVEAL THE ENTIRE EXTRAHEPATIC BILIARY TRACT...

■ Visualization achieved with Cholografin results from the high concentration of the medium attained in the bile through the prompt and rapid excretion of Cholografin by the liver; visualization is in no way dependent on absorption of the medium from the bowel or on the concentrating power of the gallbladder. ■ Provides reliable diagnostic information, both before and after surgery, on the gallbladder, on the course and calibre of the extrahepatic ducts and on the presence of stones, strictures, tumor invasion and anomalies of the ducts. ■ Filling of the gallbladder begins within an hour, permitting visualization of even the nonfunctioning gallbladder; the greatest concentrations of Cholografin are generally found in the gallbladder in 2 to 2½ hours.

Cholografin provides "... a reliable method for rapid visualization of the biliary tract irrespective of whether or not the gallbladder is present and independent of its ability to concentrate its contents." Shehadi, W.H.: *Am. J. Gastroenterol.* 28:236 (Sept.) 1957.

"When injected intravenously, [Cholografin] provides a reliable, rapid, and safe medium for visualization of the entire biliary tract, as demonstrated by our experience in over 200 cases." Shehadi, W.H.: *Intravenous cholecystocholangiography.* *J.A.M.A.* 159:1350 (Dec. 3) 1955.

Available as: Cholografin Methylglucamine (Squibb Iodipamide Methylglucamine 52% solution). Each package contains one 20 cc. ampul and one 1 cc. ampul for sensitivity testing. Cholografin Sodium (Squibb Iodipamide Sodium 20% solution). Each package contains two 20 cc. ampuls and two 1 cc. ampuls for sensitivity testing. Cholografin Methylglucamine has twice the radiopaque iodine content of Cholografin Sodium so that it provides adequate opacification in half the volume.

Squibb Iodipamide

# CHOLOGRAFIN

a reliable, well-tolerated, intravenous contrast medium

SQUIBB



Squibb Quality — the Priceless Ingredient

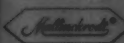
CHOLOGRAFIN® IS A SQUIBB TRADEMARK

SQUIBB





Like the sun . . . eternal and dependable . . . codeine continues its historic role in the alleviation of suffering. Physicians still turn to codeine for reliable, effective and well tolerated analgesia, plus mild sedation . . . for expectorant-sedative and soothing action in cough that nevertheless preserves the cough reflex . . . for compatibility with other drugs that makes for more versatile therapy.



MALLINCKRODT STREET  
ST. LOUIS 1, MISSOURI  
22 GOLD ST., N. Y. N. Y.

## CODEINE

A STANDARD ANALGESIC AND ANTITUSSIVE

NOW SAFER ACTIVE TRANQUILIZER THERAPY

tranquilization

anti-emetic

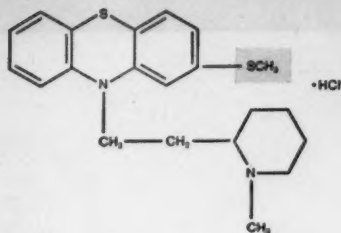
greater specificity  
of tranquilizing action  
—divorced from such  
“diffuse” effects as  
anti-emetic action  
—explains why

Mellari

THIORIDAZINE HCl

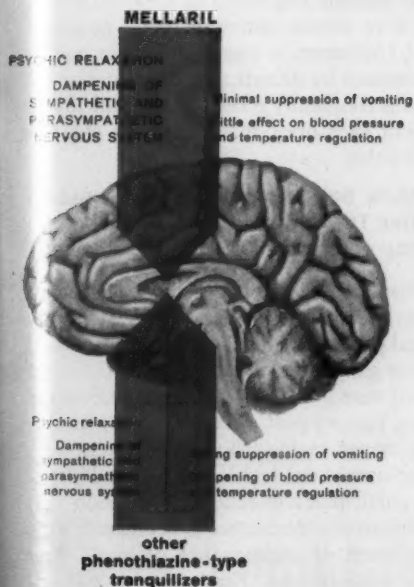
"Thioridazine [MELLARIL] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines. . . . This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."

a new advance in tranquilization:  
greater specificity of tranquilizing action results in fewer side effects



*The presence of a thiomethyl radical ( $-SCH_3$ ) is unique in Mellaril and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:*

- 1 A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.



- 2 Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.
- 3 A notable absence of extrapyramidal stimulation.
- 4 Lack of impairment of patient's normal drive and energy.
- 5 Virtual freedom from such toxic effects as jaundice, photosensitivity, skin eruptions, blood forming disorders.

Indication	Usual Starting Dose	Total Daily Dosage Range
<b>ADULTS:</b> Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneuroses, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
<b>CHILDREN:</b> BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

Mellaril Tablets, 10 mg., 25 mg., 100 mg.

\*Ortfield, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959



how often have you thought...

## "...but how will it work in my practice?"

This most frequently asked question cannot be answered by the manufacturer, the detail man, an advertisement, a piece of mail. Only through actual experience with a product in day-to-day private practice can this question be answered.

### UNITENSEN PROVED IN DAY-TO-DAY PRACTICE

In office trials, Unitensen products have been proved effective therapy in the management of the hypertensive patient. These are the facts, obtained from 3,841 physicians, who used Unitensen products in their day-to-day office practice, in treating a total of 35,727 patients. In 11,093 cases (31.0%) results were "excellent"; in 51.2% (18,294) cases, "good"; "fair" results were obtained in 4,591 patients (12.9%) and in only 1,749 cases (4.9%) were results "unsatisfactory." Minor side effects were reported in 1,081 cases (3.0%).

The results mentioned above were obtained while the patients engaged in their normal daily occupations and activities. None of the patients involved in the study were hospitalized or institutionalized. And, despite such variables as dietary indiscretions, an occasional overdose, or a dose inadvertently "missed," the Proof In Practice Study shows Unitensen products to be safe, dependable, potent antihypertensive therapy... permitting practical office management of virtually all hypertensive cases.

### UNITENSEN: BASIC HYPERTENSIVE THERAPY

Although many of the patients in the Study also received diuretics and/or tranquilizers

during the course of treatment, it was noted that the vasodilating effect of Unitensen was required to obtain optimum blood pressure control. Unitensen, a true hypotensive agent is potentiated by diuretics. A combination of the two is frequently recommended for lower dosage of each drug, minimizing the side effects of either.

**UNITENSEN DOES MORE THAN LOWER BLOOD PRESSURE** Dr. Burton M. Cohen\* makes the following observations regarding Unitensen

"Hypotensive effect obtained through specific stimulation of afferent side of reflex pathway... of blood pressure control without adrenolytic action or ganglionic blocking... Nausea and vomiting rare... No alteration of vasomotor reflexes, thus no postural collapse... Bradycardia, never tachycardia, may occur... Cardiac output not lessened... Renal circulation participates in reflex vasodilation... Cerebrovascular resistance is decreased, with improvement or maintenance of blood flow and O<sub>2</sub> utilization... No dangerous side actions have been reported."\*

**UNITENSEN-R®** Each tablet contains cryptenamine (tannates) 1.0 mg., reserpine, 0.1 mg.

**UNITENSEN-PHEN®** Each tablet contains cryptenamine (tannates) 1.0 mg., phenobarbital, 15 mg.

**UNITENSEN®** Each tablet contains cryptenamine (tannates) 2.0 mg.

*Clinical supplies available on request.*

*Neisler*

IRWIN, NEISLER & CO. • Decatur, Illinois

\*Cohen, B. M.: The Ambulatory Patient with Hypertension: An Approach to Office Management, presented at the American Medical Association Convention, San Francisco, California, June 22-27, 1958.

*for  
the  
tense  
and  
nervous  
patient*



**relief comes fast and comfortably**

- does not produce autonomic side reactions
- does not impair mental efficiency, motor control, or normal behavior.

*Usual Dosage:* One or two 400 mg. tablets t.i.d.

*Supplied:* 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS®—400 mg. unmarked, coated tablets.

**Miltown®**

meprobamate (Wallace)



**WALLACE LABORATORIES / New Brunswick, N. J.**

Compazine<sup>®</sup> can help you relieve the suffering  
brand of prochlorperazine

# TENSION HEADACHE



Tension headache is one of many stress symptoms that promptly respond to 'Compazine'.<sup>1,2,3</sup>

Other symptoms benefited by Compazine's unique nonsedative calming action are functional g.i. complaints, generalized musculoskeletal pain, anorexia and insomnia.

For convenient daylong or nightlong effect with a single oral dose, prescribe 'Compazine' Spansule® sustained release capsules.

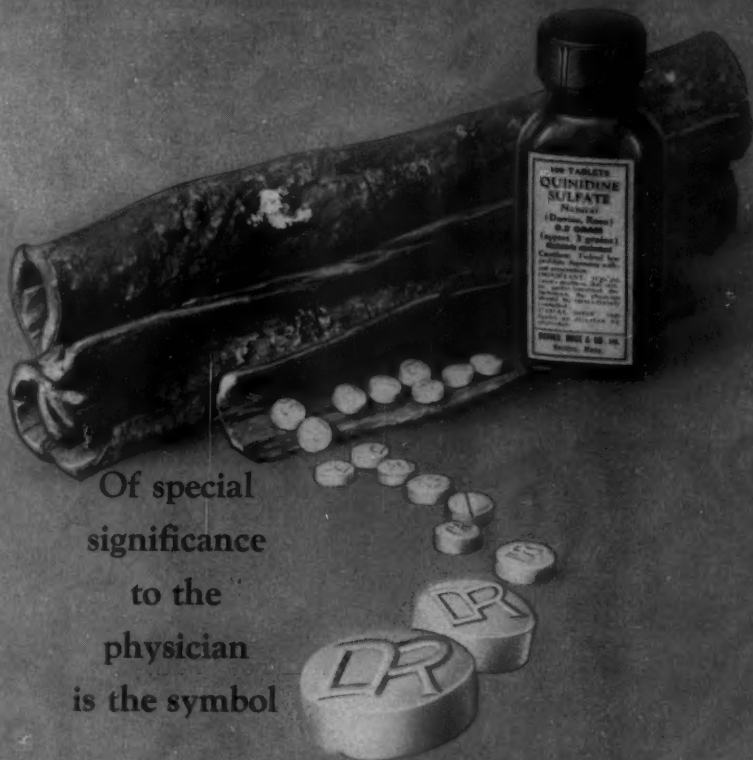
Also available: Tablets, Syrup, Suppositories, Ampuls and Multiple dose vials.



SMITH KLINE & FRENCH LABORATORIES, PHILADELPHIA

1. Wennersten, J.R.: Clin. Med. 3:1179 (Dec.) 1956. 2. Settel, E.: J. Am. Geriatrics Soc. 5:827 (Oct.) 1957. 3. McAfoos, L.G., Jr.: Dis. Nerv. System 18:430 (Nov.) 1957.





Of special  
significance  
to the  
physician  
is the symbol

When he sees it engraved on a Tablet of Quinidine Sulfate he has the assurance that the Quinidine Sulfate is produced from Cinchona Bark, is alkaloidally standardized, and therefore of unvarying activity and quality.

When the physician writes "DR" (Davies, Rose) on his prescriptions for Tablets Quinidine Sulfate he is assured that this "quality" tablet is dispensed to his patient.

Rx Tablets Quinidine Sulfate Natural

0.2 Gram (or 3 grains)

Davies, Rose

*Clinical samples sent to physicians upon their request*

Davies, Rose & Company, Limited  
Boston 18, Mass.

O-7



**more dependable absorption for more predictable results in  
HYPERTENSION**

Protalba-R contains protoveratrine A,\* a single alkaloid of veratrum for more effective management of the hypertensive patient.

Protoveratrine A reduces elevated blood pressure with more predictable results than ever before possible in oral veratrum therapy because of its crystalline purity and ready absorption from the intestinal tract.

Combination of protoveratrine A with crystalline reserpine in Protalba-R permits blood pressure reduction with smaller and thus better tolerated doses than when either drug is used alone.

**protalba-R<sup>†</sup>**

<sup>†</sup>Trademark for Tablets Protoveratrine A, 0.2 mg. and Reserpine, 0.08 mg. \*Patent Pending



**PITMAN-MOORE COMPANY** Division of Allied Laboratories, Inc., Indianapolis 6, Indiana



**ANTISPASMODIC  
ANTISECRETORY  
TRANQUILIZER**

**One preparation for multiple G.I. symptoms** — ENARAX combines a new long-acting anticholinergic, oxyphen-cyclimine, with the proven antisecretory tranquilizer, ATARAX, to relieve pain, spasm, hyperacidity and tension associated with organic disturbances.

**Two tablets daily for full-time relief** — ENARAX successfully controlled symptoms in 94% of reported cases. In the majority of patients, two tablets daily in divided doses provided 24-hour control.

**Relatively free of side effects** — Side effects seldom consist of more than dryness of the mouth. Selective postganglionic action on the G.I. tract keeps adverse reactions to a minimum.<sup>4</sup>

**SUMMARY OF CASES**

**Clinical Diagnosis** — Peptic Ulcer — Gastritis — Gastroenteritis — Colitis — Functional Bowel Syndrome — Duodenitis — Hiatus Hernia (Symptomatic) — Irritable Bowel Syndrome — Pylorospasm — Cardiospasm — Biliary Tract Dysfunctions

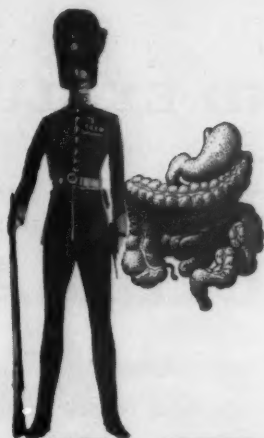
<b>Clinical Results</b>	<b>Oxyphen-cyclimine<sup>1,2</sup></b>	<b>ENARAX<sup>3,4</sup></b>
Effective	491 (88%)	223 (94%)
Failure	68 (12%)	15 (6%)
<b>Total number of cases</b>	<b>559</b>	<b>238</b>

**Each ENARAX tablet contains:**

Oxyphen-cyclimine HCl .....10 mg.  
Hydroxyzine (Atarax®) .....25 mg.

**Dosage:** One-half to one tablet twice daily—preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy and with ophthalmological supervision in glaucoma.

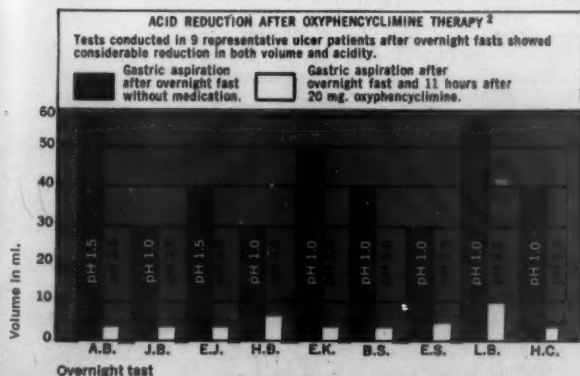
**Supplied:** in bottles of 60 black-and-white scored tablets.



# ENARAX®

(oxyphenyclimine plus ATARAX®)

## A SENTRY FOR THE G.I. TRACT



References: 1. Stelgmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois: in press. 2. Winkelstein, A.: *Am. J. Gastroenterol.* 32:66 (July) 1959. 3. Data in Roerig Medical Department files. 4. Leming, B. H., Jr.: *Clin. Med.* 6:423 (Mar.) 1959.

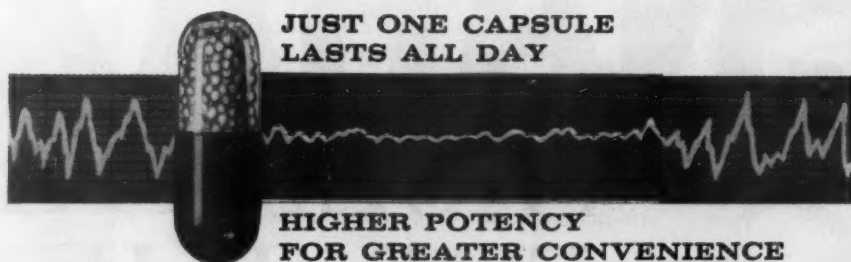


New York 17, N. Y.  
Division, Chas. Pfizer & Co., Inc.  
Science for the World's Well-Being

# NEW AND EXCLUSIVE FOR SUSTAINED TRANQUILIZATION

MILTOWN® (*meprobamate*) now available  
in 400 mg. continuous release capsules as

## Meprospan®-400



- relieves *both* mental and muscular tension without causing depression
- does not impair mental efficiency, motor control, or normal behavior

**Usual dosage:** One capsule at breakfast,  
one capsule with evening meal

**Available:** *Meprospan-400*, each blue capsule contains  
400 mg. Miltown (*meprobamate*)  
*Meprospan-200*, each yellow capsule contains  
200 mg. Miltown (*meprobamate*)  
*Both potencies in bottles of 30.*

**W** WALLACE LABORATORIES, *New Brunswick, N. J.*

CHE-8437



# DIASAL

doubly valuable for patients on salt-restricted diets

Besides encouraging the patient's adherence to diet, DIASAL offers pleasant-tasting prophylaxis against the potassium loss incurred by the use of the more recent oral diuretics. The potassium supplementation, concurrently supplied by DIASAL, helps avoid digitalis toxicity due to urinary loss of this ion. Constituents: Potassium chloride, glutamic acid and inert excipients. Available in 2-ounce shakers and 8-ounce bottles.

**FOUGERA** E. FOUGERA & CO., INC., Hicksville, Long Island, New York

41999

*announcing*

**A CHANGE  
IN NAME**

# SURFAK<sup>\*</sup> FORMERLY DOXICAL

## A NEW CHEMICAL SUPERIOR FECAL SOFTENER

**SURFAK** (formerly **Doxical**) the new therapeutic chemical, calcium bis-(dioctyl sulfosuccinate) represents a markedly more efficient surfactant softening agent than the older fecal softening chemicals.

■ optimal fecal homogenization ■ greater surfactant effectiveness ■ non-laxative  
■ normal physiologic action—no effect on the bowel itself ■ non-habit forming ■ Sodium free

**USUAL ADULT DOSE:** 240 mg. daily. Children and adults (with minimum needs) 50 to 150 mg. daily.

**SUPPLIED:** Surfak 240 mg. capsules—bottles of 15 and 100. Surfak 50 mg. capsules—bottles of 30 and 100.

**LLOYD BROTHERS, INC. CINCINNATI 3, OHIO**

\*Patent Pending

Bright  
new  
star



in the  
antibacterial  
firmament

the first nitrofuran  
effective orally  
in systemic bacterial infections

**ALTAFUR** T. H.  
brand of furaltadone

*Effective clinically in upper respiratory infections,  
pneumonias, soft tissue infections, bacteremia/septicemia,  
osteomyelitis, wound infections and pyodermas.*

Effective in vitro against the following organisms (isolated from clinical infections listed above):

Organism	Sensitive	Resistant	% Sensitive
Staphylococci*	181	1	99.4
Streptococci	65	1	98.5
D. pneumoniae	14	0	100.0
Coliforms	34	3	91.8
Proteus	5	5	50.0
A. aerogenes	8	0	100.0
Ps. aeruginosa	5	4	55.5

\*Includes many strains resistant to antibiotics.

As with all nitrofurans in years of extensive clinical use, there is little or no development of bacterial resistance with ALTAFUR.

NITROFURANS—a unique class of antimicrobials—  
neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK



REFLECTION ON  
CORTICOTHERAPY:

The clinical aim, following immediate suppression of disease symptoms, is to maintain the patient symptom-free... with minimal side effects.

The logical course is to select the steroid with the best ratio of desired effects to undesired effects:

the corticosteroid that hits the disease, but spares the patient

**Upjohn**

THE UPJOHN COMPANY  
KALAMAZOO, MICHIGAN

\*TRADEMARK, REG. U. S. PAT. OFF. — METHYLPREDNISOLONE, UPJOHN



**Medrol\***

## CLINICAL NOTES

### HEMATOLOGY

#### A NEW INTRAVENOUS IRON COMPLEX

##### ASTRAFER<sup>®</sup> (ASTRA) I.V.

**COMPOSITION** A soluble, high-molecular, iron carbohydrate complex, equivalent to 20 mg. trivalent iron per cc., not to be confused with saccharated iron complexes.

**PROPERTIES** ASTRAFER<sup>®</sup> I.V. is a neutral solution and does not irritate the intima. It is relatively free from the side reactions previously encountered with other intravenous iron preparations. 70-100% of the iron supplied by this agent is utilized in hemoglobin synthesis. Patient improvement is marked by a measurable sense of well being, and is seen coincidentally with the return to normal of serum iron and hemoglobin levels, usually beginning with the third or fourth injection.

**INDICATIONS** Severe iron deficiency anemia characteristic of late pregnancy and massive or repeated blood loss, where rapid replenishment of large iron deficits is mandatory, and wherever orally administered iron may be either ineffective or poorly tolerated. To date, there is no evidence that this agent is of any value in anemias of polyarthrititis or chronic nephritis. **CONTRAINDICATIONS** are pernicious anemia, leukemia or bone marrow depression, and liver damage.

**DOSAGE** Initially, 1.5 cc. (30 mg.) to be administered slowly via the intravenous route. Patient should rest 15-30 minutes after each injection. Subsequent dosage increased according to instructions found in literature \* accompanying each package.

**SUPPLIED** 5 cc. color-break ampules, boxes of 10

## ASTRAFER<sup>®</sup> (ASTRA) I.V.

\*Further information including clinical background and detailed dosage instructions available to physicians on request.

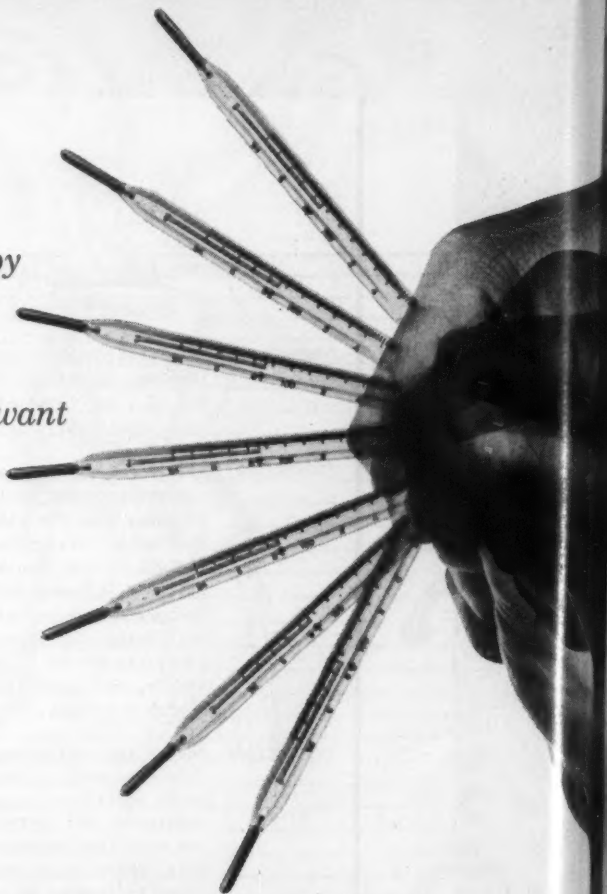
ASTRA PHARMACEUTICAL PRODUCTS, INC.  
Worcester, Mass. U. S. A.



*in oral penicillin therapy*

*the speed of action you want*

*the reliability you need*



Penicillin, still the most frequently prescribed antibiotic, assumes new reliability in the form of PEN•VEE K. Tablet or Liquid PEN•VEE K may be prescribed for all infections responsive to oral penicillin . . . *including many usually treated with parenteral penicillin.*

The speed of action and reliability of oral potassium penicillin V have been dramatically demonstrated by recent studies<sup>1,2</sup> in which 107 subjects were each given 400,000 units of the antibiotic. Appreciable penicillin levels were consistently produced within 15 minutes; peak levels within one-half hour. Penicillin levels still persisted in all subjects at two hours, and in 93 per cent of subjects at four hours.

1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., p. 1004. 2. Wright, W.W., and Welch, H.: Antibiotic Med. 5:139 (Feb.) 1958.

**PEN•VEE® K**



Philadelphia 1, Pa.

Liquid: Penicillin V Potassium for Oral Solution;  
Tablets: Penicillin V Potassium, Wyeth

**SUPPLIED:** *Liquid:* raspberry-flavored, 125 mg. (200,000 units) per 5-cc. teaspoonful; peach-flavored, 250 mg. (400,000 units) per 5-cc. teaspoonful. Both supplied as vials of powder to make 40 cc. *Tablets:* 125 mg. (200,000 units) and 250 mg. (400,000 units) in vials of 36.

Please Mention this Journal when writing to Advertisers

relieves painful muscle spasm, improves mobility, facilitates rehabilitation...

# PARAFLEX<sup>®</sup>

Chlorzoxazone<sup>®</sup>

PARAFLEX provides effective skeletal muscle relaxation for about 6 hours with a 1- to 2-tablet dose. It relieves pain and stiffness and improves function in a wide variety of orthopedic, arthritic, and rheumatic disorders. It may be used alone or with other agents indicated in the management of skeletal muscle spasm. It is especially valuable when used in conjunction with physiotherapy ● and other rehabilitative procedures. Side effects are rare, almost never require discontinuance of therapy.

**Dosage:** ADULTS—1 to 2 tablets three or four times a day.

CHILDREN— $\frac{1}{2}$  to 2 tablets three or four times a day, depending on age and weight.

**Supplied:** Tablets, scored, orange, bottles of 50. Each tablet contains PARAFLEX, 250 mg.

U.S. Patent Pending

885A59



**McNEIL**

McNeil Laboratories, Inc.  
Philadelphia 32, Pa.

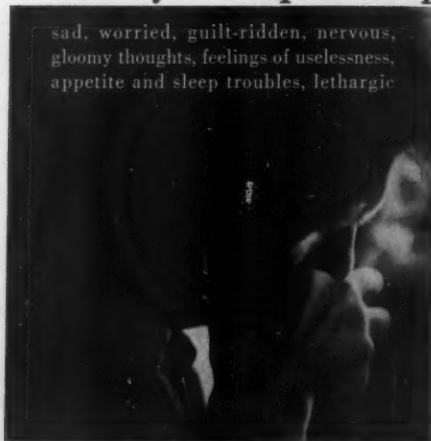
now...correct depression safely and rapidly in everyday office practice

# Nardil™

brand of phenelzine dihydrogen sulfate

restores your depressed patient to purposeful reality

sad, worried, guilt-ridden, nervous,  
gloomy thoughts, feelings of uselessness,  
appetite and sleep troubles, lethargic



safely

No significant reports of toxicity to liver, kidneys or blood<sup>1-3</sup> in thousands of cases to date.

rapidly

Antidepressant activity within the first few days; complete recovery occurs within 2 to 6 weeks.

correctively

Removes the depression itself, does not merely mask the symptoms as do tranquilizers and sedatives.

Nardil is indicated in the office treatment of all mild to severe depressions; in those related to childbirth, menopause, old age, or those caused by stress situations; when there is a past history of depressed periods, and in depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis.

**Dosage:** One tablet three times a day.

The above dosage should be maintained until remission of symptoms is achieved which may require 2 to 6 weeks. Dosage should then be

reduced to a maintenance level of one or two tablets a day.

**Supplied:** 15 mg. orange-coated tablets, bottles of 100.

**References:** 1. Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. 2. Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System* 20:197 (May) 1959. 3. Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* (in press) 1959.



MORRIS PLAINS, N.J.

Please Mention this Journal when writing to Advertisers

wherever the **4** winds blow

new **4**mg.

**POLARAMINE®**  
**REPETABS®**

For day-to-day  
relief & maintenance  
in allergic reactions

Schering



SYMBOL OF THE  
ONE-DOSE CONVENIENCE  
YOU WANT  
FOR YOUR PATIENT.

SCHERING CORPORATION • BLOOMFIELD, N.J. EN1496-9

IN  
gastritis

KEEPS THE  
MIND OFF THE  
STOMACH....  
THE STOMACH  
FREE OF PAIN

**Milpath**

Miltown + anticholinergic

relieves anxiety and tension  
for enhanced antispasmodic effect



WALLACE LABORATORIES

IMPORTANT NEW PSYCHOACTIVE AGENT



**Catron**

Diethylmagnesium pyrazine succinate (Catron succinate)

For complete information send for Brochure No. 19 CATRON

**L**

WALLACE LABORATORIES, INC.  
MILWAUKEE 1, WISCONSIN

50259





you  
control  
more  
than  
high  
blood pressure  
with

# Serpasil-Esidrix

Combination Tablets

## POTENTIATED ANTIHYPERTENSIVE

Serpasil-Esidrix not only lowers blood pressure, it controls complications of hypertension, too. For example, it rapidly eliminates excess fluid in decompensated patients with edema. And, through its heart-slowng and calming actions, Serpasil-Esidrix also relieves the tachycardia and anxiety that so often accompany hypertension. Equally important: Esidrix combined with Serpasil frequently reduces pressure to lower levels than single-drug therapy. Potentiated antihypertensive effect—single-tablet convenience. SUPPLIED: *Tablets* (light orange, scored), each containing 0.1 mg. Serpasil and 25 mg. Esidrix. SERPASIL®-ESIDRIX® (reserpine and hydrochlorothiazide CIBA)



07-204666

CIBA  
SUMMIT • NEW JERSEY

Please Mention this Journal when writing to Advertisers



When cough causes strain and trauma...in the elderly and debilitated; in patients with pulmonary and cardiac disease, hernia or rib fracture; in EENT, chest and abdominal surgery...with ROMILAR you can provide the antitussive potency of codeine with the safety of a placebo.<sup>1-9</sup> Cough control is prompt (15-30 minutes) and lasts for as long as six hours.<sup>1</sup>

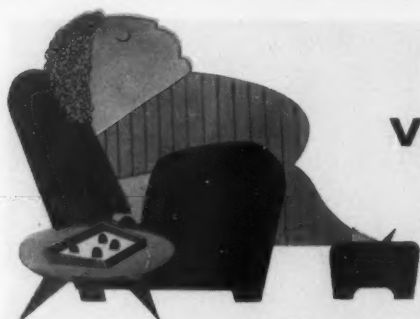
**ROMILAR, the non-narcotic cough specific,** has one pharmacologic action—cough suppression. There is no central depressant or analgesic effect; and there is no tolerance liability, no addictive potential.<sup>2-9</sup>

**Bibliography:** (1) N. Ralph, *Am. J. M. Sc.* 227:297, 1954. (2) H. A. Bickerman, in W. Modell, Ed., *Drugs of Choice 1958-1959*, St. Louis, The C. V. Mosby Company, p. 557. (3) H. A. Bickerman, E. German, B. M. Cohen and S. Itkin, *Am. J. M. Sc.* 234:191, 1957. (4) L. J. Cass, W. S. Frederik and J. B. Andosca, *Am. J. M. Sc.* 227:291, 1954. (5) L. J. Cass and W. S. Frederik, *J. Lab. & Clin. Med.* 48:879, 1956. (6) L. J. Cass and W. S. Frederik, *New England J. Med.* 249:132, 1953. (7) H. Isbell and H. F. Fraser, *J. Pharmacol. & Exper. Therap.* 107:524, 1953. (8) W. M. Benson, P. L. Stefko and L. O. Randall, *J. Pharmacol. & Exper. Therap.* 109:189, 1953. (9) *New and Nonofficial Drugs 1959*, Philadelphia, J. B. Lippincott Company, p. 326.

**Supply:** ROMILAR Syrup in bottles of 4 oz, 16 oz and 1 gal. ROMILAR Tablets in bottles of 20, 100 and 500. Romilar® Hydrobromide—brand of dextromethorphan hydrobromide.

**ROCHE LABORATORIES** • Division of Hoffmann-La Roche Inc • Nutley 10, N. J.

# Romilar



## Victim of Overeating and "Oversitting"

Rx

# BIPHETAMINE®

A 'STRASONIC' RELEASE ANORETIC

RESIN

- 10-14 Hour Appetite Curb
- 10-14 Hour Mild Invigoration
- Predictable Weight Loss ...  
a comfortable 1 to 3 lbs. a week in 9 out of 10 cases

In many instances both appetite limitation and mild invigoration ('Biphetamine') are required to effect the balance between caloric intake and energy output necessary for predictable weight reduction and control. Since 'Straslonic' release is employed, the desired therapeutic action is uniform, predictable and comfortable.



### BALANCE

Biphetamine may be prescribed for obese patients who are hypertensive, arthritic, diabetic, pregnant, menopausal, aged; and to reduce surgical risks. Use with initial care in patients hypersensitive to sympathomimetic compounds, in cases of coronary disease or severe hypertension.

- Single Capsule Daily Dose 10 to 14 hours before retiring

3

STRENGTHS

List No. 875

**BIPHETAMINE®**  
 '20' Resin

Each black capsule contains:  
 d-amphetamine ..... 10 mg.  
 dl-amphetamine ..... 10 mg.  
 as resin complexes



List No. 876

**BIPHETAMINE®**  
 '12½' Resin

Each black and white capsule contains:  
 d-amphetamine ..... 6.25 mg.  
 dl-amphetamine ..... 6.25 mg.  
 as resin complexes



List No. 895

**BIPHETAMINE®**  
 '7½' Resin

Each white capsule contains:  
 d-amphetamine ..... 3.75 mg.  
 dl-amphetamine ..... 3.75 mg.  
 as resin complexes



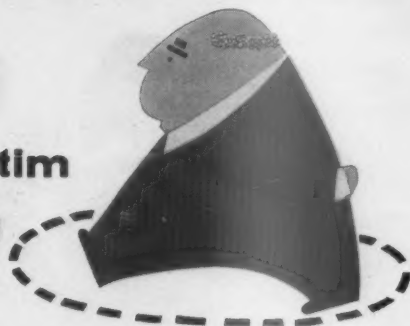
Rx Only. Caution: Federal law prohibits dispensing without prescription.

Biphetamine—made and marketed ONLY by

**STRASBURGH LABORATORIES**  
 ROCHSTER, N.Y., U.S.A.

Originators of 'Straslonic' (sustained ionie) Release

Victim  
of Overeating



Rx **NEW**

**Non-Amphetamine**

# IONAMIN<sup>TM</sup>

'STRASIONIC' ANORETIC

PHENYL-TERT.-BUTYLAMINE RESIN

- **10-14 Hour Appetite Curb**
- **Predictable Weight Loss...**  
a comfortable .221 lbs. per day in average case



**BALANCE**

In many instances, appetite limitation only ('Ionamin') is required to effect the balance between caloric intake and energy output necessary for predictable weight reduction and control. Since 'Strasionic' release is employed, the desired therapeutic action is uniform, predictable and comfortable.

Ionamin may be prescribed for obese patients who are arthritic, diabetic, pregnant, menopausal, aged, to reduce surgical risks, and may be used with caution in hypertensive or cardiovascular disease.

- **Single Capsule Daily Dose 10 to 14 hours before retiring**

**2** STRENGTHS

List No. 904

**IONAMIN<sup>TM</sup>**  
**'30'**

Each yellow capsule contains:  
phenyl-tert.-butylamine . . . 30 mg.  
as a resin complex



List No. 903

**IONAMIN<sup>TM</sup>**  
**'15'**

Each gray and yellow capsule contains:  
phenyl-tert.-butylamine . . . 15 mg.  
as a resin complex



Rx Only.  
Caution: Federal law prohibits  
dispensing without prescription.

Ionamin—made and marketed ONLY by

**STRASBURGH LABORATORIES**  
ROCHESTER, N.Y., U.S.A.

Originators of 'Strasionic' (sustained ionic) Release



## Help for cough victims

Stop Cough 8-12 Hours with a Single Dose

# Rx TUSSIONEX<sup>®</sup>

A 'Strasionic' Antitussive • Dihydrocodeinone Resin—Phenyltoloxamine Resin

- A Single Dose Controls Cough for 8-12 Hours
- Permits Natural Discharge of Mucous
- Uninterrupted Antitussive Action with Minimum Amount of Narcotic Through 'Strasionic' Release

TWO FORMS: Tussionex Thixaire™ Suspension • Tussionex Tablets


Each teaspoonful (5c.c.) or tablet provides 5 mg. dihydrocodeinone and 10 mg. phenyltoloxamine as resin complexes.

Dose: 1 teaspoonful or tablet q 12 h. Children under 1 year, ¼ teaspoonful q 12 h; 1-5 years, ½ teaspoonful q 12 h.

Rx only. Class B taxable narcotic.

Tussionex—made and marketed only by

**STRASBURGH LABORATORIES**  
ROCHESTER, N.Y., U.S.A.  
Originators of 'Strasionic' (sustained ionic) Release



Within 30 minutes,  
Pyridium's unusually prompt  
analgesic action will  
spare needless pain and help  
overcome resistance to  
urological procedures. When  
prescribed for home use,  
Pyridium encourages more  
normal micturition  
by removing the penalties  
of pain and burning.

**DOSAGE:** *Adults:* 2 tablets,  
(100 mg. each), three times  
daily, before meals.

*Children 9 to 12 years:*  
1 tablet three times daily  
before meals.

spare  
needless  
urinary  
pain



MORRIS PLAINS, N. J.

**PYRIDIUM®**  
(brand of phenylazo-diamino-pyridine HCl)

**SAFER,  
MORE EFFICIENT  
BETTER TOLERATED**

**QUINIDINE  
THERAPY<sup>1-3</sup>  
IN CARDIAC  
ARRHYTHMIAS**



*b.i.d. dosage*



**Safer and more efficient** because there is no let-down in plasma levels where arrhythmias tend to recur. **Better tolerated** because quinidine gluconate is ten times as soluble as quinidine sulfate—and so is easier on the g.i. tract. **Quinaglute Dura-Tab S.M. every 12 hours** maintains uniform, effective plasma levels around the clock.

## QUINAGLUTE<sup>TM</sup> DURA-TAB<sup>®</sup> S.M.

**A quinidine of choice in atrial fibrillation, flutter, premature contractions, auricular tachycardia.**

**DOSAGE:** for conversion of auricular fibrillation to normal sinus rhythm, in most cases, 2 Quinaglute Dura-Tab S.M. tablets 3 to 4 times a day, for 2 to 3 days; longer periods are required in some patients... for maintenance 1 to 2 tablets every 10 to 12 hours. Bottles of 30, 100 and 250.

1. Bellet, S.; Finkelstein, D., and Gilmore H.: A.M.A. Archives Int. Med. 100:750, 1957.

2. Bellet, S.: Amer. Heart J. 56:479, 1958.

3. Finkelstein, D.: Penn. Med. J. 61:1214, 1958.

*exclusive oral Sustained Medication\*  
Quinidine Gluconate (5 gr.)*

for samples and literature write...

**WYNN PHARMACAL CORPORATION**  
5119 West Stiles Street, Philadelphia 31, Pa.

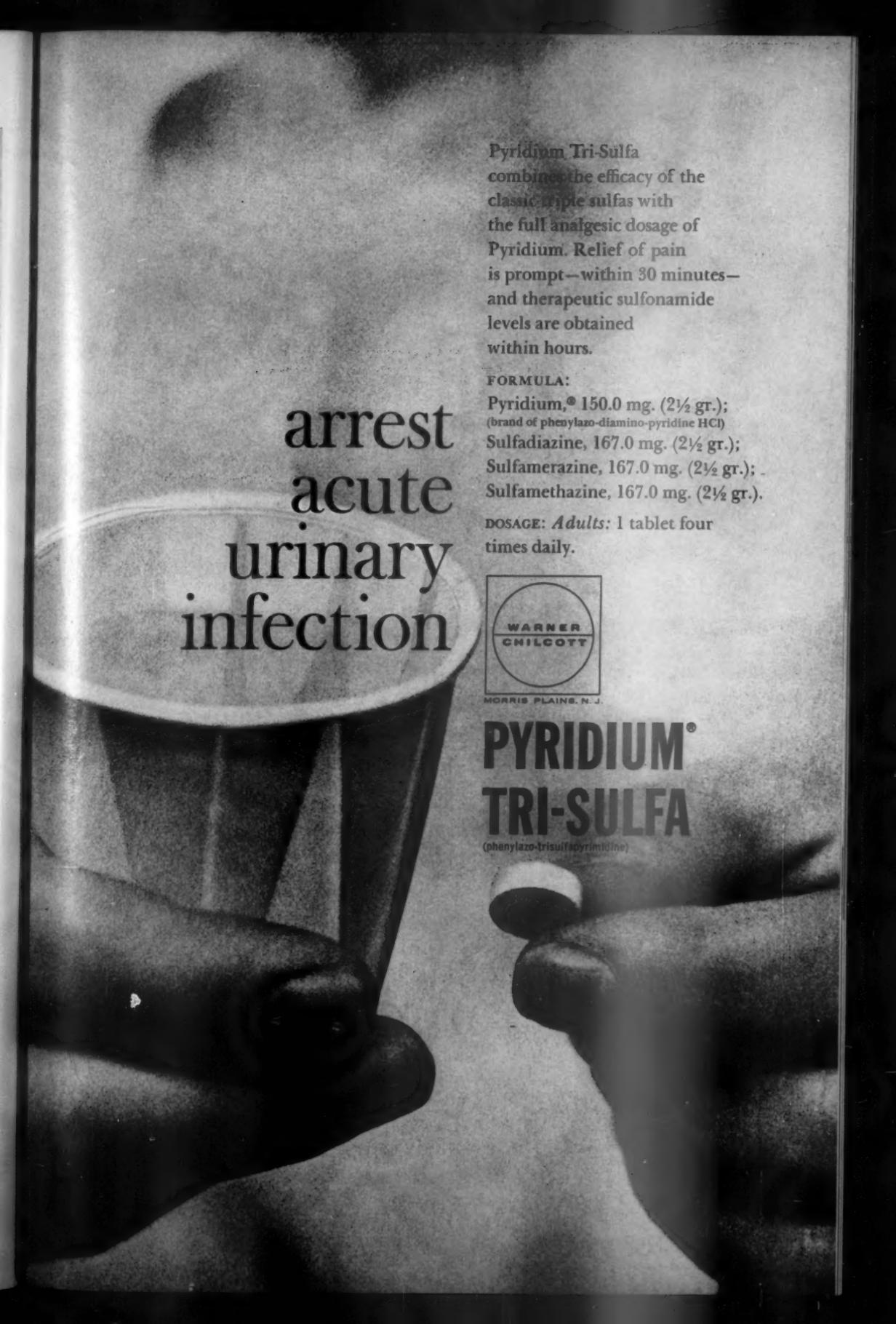
also available:

**INJECTABLE QUINAGLUTE** 10 cc. Multiple Dose Vials, 0.08 Gm. Quinidine Gluconate per cc.

\*U. S. Patent 2895881



PAGE 867



arrest  
acute  
urinary  
infection

Pyridium Tri-Sulfa combines the efficacy of the classic triple sulfas with the full analgesic dosage of Pyridium. Relief of pain is prompt—within 30 minutes—and therapeutic sulfonamide levels are obtained within hours.

FORMULA:

Pyridium,<sup>®</sup> 150.0 mg. (2½ gr.);  
(brand of phenylazo-diamino-pyridine HCl)  
Sulfadiazine, 167.0 mg. (2½ gr.);  
Sulfamerazine, 167.0 mg. (2½ gr.);  
Sulfamethazine, 167.0 mg. (2½ gr.).

DOSAGE: *Adults:* 1 tablet four times daily.



MORRIS PLAINS, N. J.

**PYRIDIUM<sup>®</sup>**  
**TRI-SULFA**

(phenylazo-trisulfapyrimidine)





*"I seem to have the blues all the time...  
I can't sleep..."*

in the depressed, unhappy patient

## PROMPTLY IMPROVES MOOD

*without* excitation

- Acts fast to relieve depression and its common symptoms: sadness, crying, anorexia, listlessness, irritability, rumination, and insomnia.
- Restores normal sleep—without hang-over or depressive aftereffects. Usually eliminates need for sedative-hypnotics.

**EFFICACY AND SAFETY CONFIRMED IN OVER 3,000  
DOCUMENTED CASE HISTORIES.<sup>1,2,3</sup>**

**Dosage:** Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

**Composition:** Each light-pink, scored tablet contains 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

**References:**

1. Alexander, L.: J.A.M.A. 166:1019, March 1, 1966.
2. Current personal communications; in the files of Wallace Laboratories.
3. Pennington, V.M.: Am. J. Psychiat. 118:280, Sept. 1961.



for depression

# Deprol<sup>†</sup>

WALLACE LABORATORIES, New Brunswick, N. J.

†mop-nam

69-0149

# control chronic urinary infection

Mandelamine's therapeutic distinction stems from its ability to control chronic urinary infections, including those resistant to antibiotics.

Mandelamine suits all age groups but it is particularly useful in older patients. Its antibacterial action is confined to the urinary tract; sensitization is unlikely; no fluids or alkalies are needed and cost is most economical.

**DOSAGE:** *Adults:* Average initial dosage is 1.0 to 1.5 Gm. four times daily.  
*Children over five:* 0.5 Gm. four times daily.



MORRIS PLAINS, N. J.

## MANDELAMINE®

(brand of methenamine mandelate)



## When the distraction is intestinal . . .

Motion study of the man in the second row rightly but sadly speaks of diarrhea. And yet intestinal repose could be his lot with POLYMAGMA. For POLYMAGMA contains Claysorb, which is more than five times as adsorptive as kaolin. It enlists two antibiotics working synergistically. It permits a low-dose regimen with high effectiveness. And it has a taste and texture that wear well all through treatment.

In noninfectious diarrhea, you would, of course, prescribe POLYMAGMA Plain, having the same formula but without antibiotics.

# Polymagma<sup>®</sup>

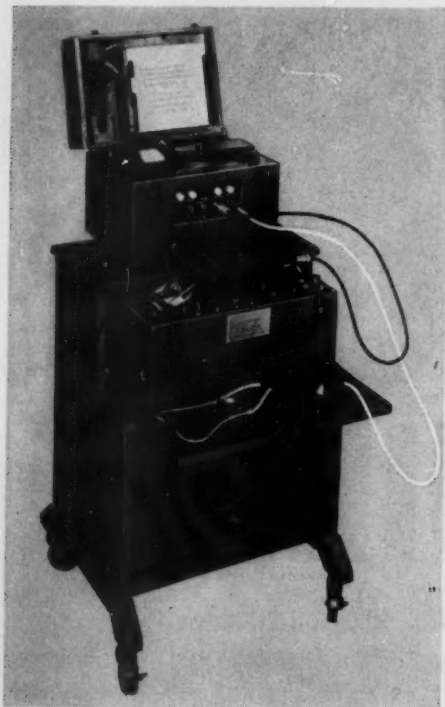
Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb\*  
(Activated Attapulgit, Wyeth) in Alumina Gel



Philadelphia 1, Pa.

\*Trademark

## To Aid the Cardiologist in making MORE ACCURATE · MORE COMPLETE Diagnosis of Heart Disease



**THE CAMBRIDGE AUDIO-VISUAL  
HEART SOUND RECORDER AND  
THE CAMBRIDGE VERSA-Scribe  
ELECTROCARDIOGRAPH**

shown mounted on a special  
space-saving Two-Tier Table.

### **CAMBRIDGE AUDIO-VISUAL HEART SOUND RECORDER**

With this portable instrument the Doctor hears the amplified heart sounds through binaural ear phones, while he views their pattern on a long persistence cathode tube screen. What he sees and hears may be permanently recorded on a paper-thin magnetic disc. Such records may be filed with the patient's history, mailed to a consultant or played back for future study.

### **CAMBRIDGE VERSA-Scribe ELECTROCARDIOGRAPH**

This accurate, portable direct-writing instrument has the CAMBRIDGE dual paper speed feature. The operator can double the speed of paper travel by simply throwing a switch. This is especially valuable when high accuracy is required for measuring intervals upon electrocardiograms showing rapid heart rates or those having notching and splintering.

*While both of these fine instruments are effectively used independently, when used together they provide a new and valuable approach to the more accurate and complete diagnosis of heart disease. Let us give you further information about them.*

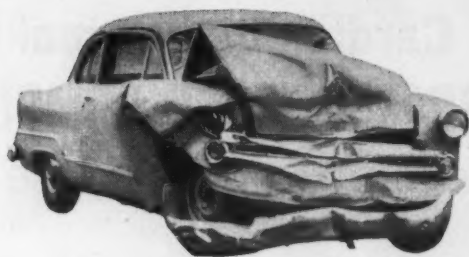
Send for bulletins #185 and #188VS

**CAMBRIDGE  
DIAGNOSTIC  
INSTRUMENTS**

### **CAMBRIDGE INSTRUMENT CO., INC.**

3777 Grand Central Terminal, New York 17, N.Y.

Cleveland 2, Ohio    Detroit 2, Mich.    Oak Park, Ill.    Jenkintown, Pa.    Silver Spring, Md.  
8419 Lake Avenue    7410 Woodward Avenue    6605 West North Avenue    479 Old York Road    933 Gist Avenue  
PIONEER MANUFACTURERS OF THE ELECTROCARDIOGRAPH



**"...safety and practicality...recommend its use in the treatment of shock."**

# SHOCK

INJECTION

# ARAMINE®

BITARTRATE

(metaraminol bitartrate)

**a superior vasopressor with a choice of routes for optimal response—no tissue slough observed<sup>2,4</sup>**

ARAMINE rapidly raises and maintains blood pressure in shock. Simplicity of administration with reported freedom from tissue slough, necrosis or thrombophlebitis<sup>1-4</sup> encourages its prompt use. Patients respond with increased glomerular filtration rate, renal blood flow and urinary output. Vasopressor effect is smooth and sustained with no secondary fall in blood pressure and no tachyphylactic response to repeated injections.

Versatile ARAMINE is indicated in shock accompanying anaphylaxis, myocardial infarction, brain damage and infectious disease, as well as hypotension due to hemorrhage, surgery and other factors that lead to shock.

supplied in 1-cc. ampuls and 10-cc. vials (10 mg. per cc.).

references: 1. Am. J. M. Sc. 238:357, Oct. 1955.  
2. Circulation 16:1096, Dec. 1957.

3. Circulation 13:834, June 1956.  
4. J.A.M.A. 163:1482, April 20, 1957.

ARAMINE is a trademark of Merck & Co., Inc.



MERCK SHARP & DOHME

Division of Merck & Co., Inc. Philadelphia 1, Pa.

# The "ANNALS" . . . .

*"The most popular journal of internal medicine"*



The ANNALS OF INTERNAL MEDICINE was founded on July 1, 1927. It is the official journal of The American College of Physicians and the only publication providing coverage of its more than 10,500 members, each of whom is outstanding in the field of internal medicine, or one of its allied or sub-specialties. Its position as a leading periodical in the field of internal medicine is attested by its rapidly growing circulation which has passed the 23,263 mark.

The "ANNALS" serves as the medium for the publication of important contributions by authorities both from within and without the College membership, in this country and abroad. The cultural side of medicine, as well as the scientific and purely clinical, is represented. In recent years a feature of each issue in this journal has been a section on Case Reports and significant papers from the Annual Sessions and Regional Meetings of the College.

## The "ANNALS" contains . . .

- **BOOK REVIEWS**—of important fields in internal medicine by acknowledged authorities.
- **NEWS NOTES**—activity of the College, its members, matters of national and international medical interest.
- **EDITORIALS**—on subjects of special interests to the readers.
- **INTERLINGUA SUMMARY**—for readers who do not read English fluently.
- **ADVERTISING**—specifically related to internal medicine and its allied fields, selected publishers of medical books, periodicals, manufacturers of reliable instruments, pharmaceuticals and other therapeutic products.

**PUBLISHED MONTHLY**—two volumes per annum, starting January and July.

**SUBSCRIPTION RATES**—price per annum, net postpaid: \$10.00, United States, Canada, Hawaii, and Puerto Rico; \$7.00 in the above countries to bona fide medical students, interns, residents and fellows-in-training (certified in writing by the institutions); \$12.00, other countries; Single copies \$1.25; current volume when available.

---

The American College of Physicians  
4200 Pine Street  
Philadelphia 4, Pa.

Please enter my subscription to the ANNALS OF INTERNAL MEDICINE beginning with the ..... number.

I enclose ☐ Money Order; ☐ Check for \$.....

Name.....

Address.....

City..... Zone..... State.....

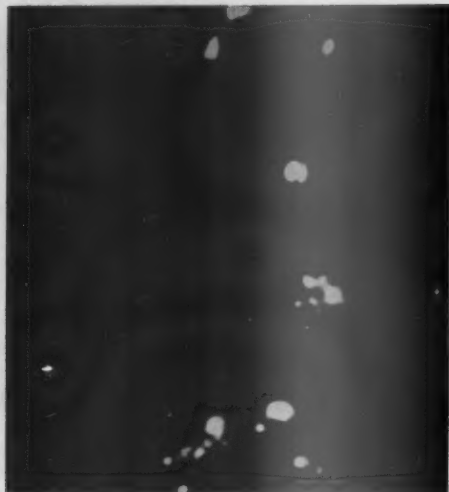
Subscriptions accepted either on Volume or Annual basis. New volumes start January and July. Subscribers claiming entitlement to the reduced rate must submit certification from their institutions, mentioning inclusive dates of appointments.

Please Mention this Journal when writing to Advertisers

# Clarín\* can do this for your postcoronary patients



**WITHOUT CLARIN**, turbid blood serum five hours after a fat meal: This unretouched dark-field photomicrograph (2500X) shows potentially hazardous fat concentrations circulating in the blood stream of a patient after a standard fat meal.



**WITH CLARIN**, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

**CLARIN** is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of postprandial lipemic serum."<sup>1</sup> Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.<sup>2</sup> It therefore provides important benefits for your postcoronary patients.

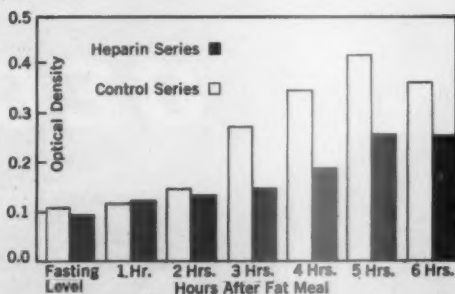
**Indication:** For the management of hyperlipemia associated with atherosclerosis.

**Dosage:** After each meal, hold one tablet under the tongue until dissolved.

**Supplied:** In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

1. Fuller, H. L.: *Angiology* 9:311 (Oct.) 1958.

2. Shaftel, H. E., and Selman, D.: *Angiology* 10:131 (June) 1959.



Average serum optical density in 36 patients after fat meal with and without sublingual heparin.<sup>2</sup>

\*Registered trade mark. Patent applied for.

*Theo. Leeming & Co., Inc.* New York 17, N. Y.

**NEW** concept

in chronic constipation...

and especially that associated with  
the irritable bowel syndrome



**DECHOTYL**

**TRABLETS\***

provides physiologic support until function returns

\*T.M. for AMES trapezoid-shaped tablet.



# DECHOTYL<sup>TM</sup>

TABLETS\*

## safe, gentle transition to normal bowel function

DECHOTYL provides gentle stimulation of the bowel and helps restore normal consistency of the intestinal contents to gradually re-establish normal bowel function in your chronically constipated patients.

**THE RATIONALE** of DECHOTYL is based on an effective combination of therapeutic agents:

**DECHOLIN®**, dehydrocholic acid, AMES, (200 mg.), the most potent hydrochol-  
eretic available, is a chemically pure bile acid and has been used effectively in the treat-  
ment of biliary tract disorders for many years. It produces an increased flow of thin bile  
which helps to lower surface tension of intestinal fluids, promotes emulsification and  
absorption of fats and mildly stimulates intestinal peristalsis.

**Desoxycholic Acid (50 mg.)**—a choleric, also is a chemically pure bile acid and  
stimulates an increased flow of bile, lowers surface tension and stimulates peristalsis.  
By emulsifying fat globules, desoxycholic acid aids the digestive action of the fat-splitting  
enzyme, lipase. DECHOLIN and desoxycholic acid thus favorably influence the constitu-  
tion and the movement of the intestinal contents.

**Diocetyl Sodium Sulfosuccinate (50 mg.)** is a wetting agent which lowers surface  
tension and aids the penetration of intestinal fluids into the fecal mass, providing a moist  
stool of normal consistency.

**EFFECTIVE:** Bile influences the constitution as well as the movement of the intes-  
tinal contents. The ingredients of major importance are DECHOLIN and desoxy-  
cholic acid which increase the flow of bile, lower surface tension, promote  
emulsification and absorption of fats and mildly stimulate intestinal peristalsis. With  
diocetyl sodium sulfosuccinate, a good therapeutic effect can be obtained without the  
danger of toxicity or decreasing effectiveness even when used regularly.

**SAFE:** Clinical evidence indicates that the constituents of DECHOTYL cause no  
systemic sensitivity, drug accumulation, habituation or interference with nutrition.  
Orally, in therapeutic amounts, DECHOTYL is without significant toxic effect. The  
only side effect following oral administration is diarrhea if the dosage is excessive.

**Dosage:** Average adult dose—Two TABLETS\* at bedtime. Some indi-  
viduals initially may require 1 to 2 TABLETS three or four times daily.  
**Contraindications:** Biliary tract obstruction; acute hepatitis.

**Available:** TABLETS,\* coated, yellow, trapezoid-shaped; bottles of 100.

**AMES**  
COMPANY, INC  
Elkhart • Indiana  
Toronto • Canada



# B & O

BELLADONNA & OPIUM • FORMULAS 15A-16A

# SUPPRETTES®

SUCCESSOR TO THE SUPPOSITORY

## Effective narcotic therapy rectally

For over 50 years Belladonna and Opium Formulas 15A and 16A have provided quick systemic relief of severe pain without side effects. The Belladonna alkaloids are in amounts sufficient to oppose the objectionable side effects of opium, especially the morphine alkaloid. These formulations are now available in Webster's water-soluble NEOCERA® base which breaks down on contact with moisture of the mucuous membrane, not temperature. No refrigeration is necessary.

Composition: Each 15A Suppnette contains 1/2 gr. Powdered Opium, U.S.P.—1/4 gr. Extract Belladonna—Each 16A Suppnette contains 1 gr. Powdered Opium, U.S.P.—1/4 gr. Extract Belladonna

Packaged 12 Suppnettes to the jar. \*Narcotic Order Required.



The William A. Webster  
Company

MEMPHIS 3, TENNESSEE

## OUR 50TH ANNIVERSARY OF PHARMACEUTICAL MANUFACTURE

Ann Woodward,  
Director

**FINE OFFICE  
FACILITIES?  
NEW QUARTERS?**

**ASSETS, ALL—**  
but the cornerstone  
of successful practice is

**the skilled physician**

ONLY *he* can supply the essential knowledge and experience. Only under *his* direction can fine equipment be made to enhance medical service.

The Woodward Bureau has helped many good practices to grow —by assistance in locating another pair of capable hands, another well trained mind. When you notify us of a personnel need, for instance, we immediately begin the search for precisely the internist or other associate you require. Then our swift, systematic notification service takes over, placing you in touch with candidates.

As we work together, you will discover how our long experience in medical placement is helping us to interpret your needs accurately, to save your time and aid in locating another skilled physician who may contribute to your own stature.

WHEN you so much as consider an addition to your office, clinic or hospital—or perhaps a change in your own future—contact us at once to explore the field for you!



**WOODWARD**  
MEDICAL PERSONNEL BUREAU  
FORMERLY AZNOES • 185 N. WABASH • CHICAGO

*Provider of the consulting service to  
the medical profession, serving medical  
with distinction over half a century*

## URGENTLY NEEDED

Back Issues of  
**ANNALS OF INTERNAL  
MEDICINE**

Due to a large demand for Vol. 49,  
No. 3 – September, 1958; Vol. 49,  
No. 4 – October, 1958; Vol. 50, No.  
1 – January, 1959; our stock for  
these issues has become completely exhausted.

We will pay \$.75 for good used  
copies.

Address Journals to:

E. R. LOVELAND, Executive Secretary  
4200 Pine Street  
Philadelphia 4, Pa.

## CLINICAL LITERATURE ON DIGITOXIN CONFIRMS...

"most widely used digitalis preparation"<sup>1</sup>

"drug of choice when a purified

digitalis product is desired"<sup>2</sup>

"the drug par excellence for oral use"<sup>3</sup>

# digitaline nativele®

the original pure crystalline digitoxin

For both initial digitalization and maintenance therapy of the cardiac patient, the steady predictable effect of DIGITALINE NATIVELLE facilitates individualized treatment. Complete absorption from the intestinal tract and uniform dissipation of DIGITALINE NATIVELLE permits easy attainment and maintenance of optimal effects.

Available in oral, intramuscular, and intravenous form with weight for weight equivalence of dosage. A product of Nativelle, Inc.

(1) Gross, H., and Jezer, A.: Treatment of Heart Disease, Philadelphia, W. B. Saunders Company, 1956, p. 41. (2) Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2., New York, The Macmillan Company, 1956, p. 698. (3) Modell, W.: Drugs of Choice 1958-1959, St. Louis, C. V. Mosby Company, 1958, p. 441.

FOUGERA

E. FOUGERA & CO., INC., HICKSVILLE, LONG ISLAND, N. Y.

HT78

Please Mention this Journal when writing to Advertisers

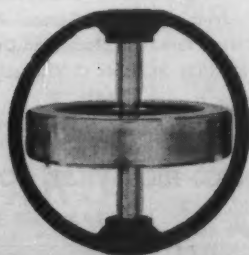
in rheumatoid arthritis...

*still unsurpassed  
for total  
corticosteroid  
benefits*

# Aris

*Substantiated by published reports of leading clinicians;*

- effective control  
of inflammatory  
and  
allergic symptoms<sup>1-9</sup>



- minimal disturbance  
of the patient's  
chemical and psychic  
balance<sup>9-17</sup>



# stocort<sup>®</sup>

Triamcinolone LEDERLE

*At anti-inflammatory and antiallergic dosage levels,  
ARISTOCORT means:*

- freedom from salt and water retention
- virtual freedom from potassium depletion
- negligible calcium depletion
- euphoria and depression rare
- no voracious appetite—  
no excessive weight gain
- low incidence of peptic ulcer
- low incidence of osteoporosis  
with compression fracture

*Precautions:* All traditional precautions to corticosteroid therapy apply. Dosage should be adjusted to the smallest amount needed to suppress symptoms.

*Supplied:* Scored tablets of 1 mg. (yellow); 2 mg. (pink); 4 mg. (white); and 16 mg. (white).  
Diacetate Parenteral (for intrasynovial and intra-articular injection). Vials of 5 cc. (25 mg./cc.);  
Diacetate Syrup, bottles of 4 fl. oz. (2 mg. per 5 cc.).

*List of References 1-17 supplied on request.*



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N.Y.

## ONE PITCH AND I STRUCK OUT...



Just an hour of pitching baseball with my son and I "threw my arm out." Painful? I couldn't even sleep that night!



Next day on the job I was a total loss—could hardly lift a slide rule!



I saw my doctor that night and got a prescription for some tablets.

# Percodan- Demi & Percodan<sup>®</sup> Salts of Dihydrohydroxycodeinone and Homatropine, plus APC Tablets

## FOR PAIN

**ACTS FASTER**—usually within 5-15 minutes. **LASTS LONGER**—usually 6 hours or more. **MORE THOROUGH RELIEF**—permits uninterrupted sleep through the night. **RARELY CONSTIPATES**—excellent for chronic or bedridden patients. **VERSATILE**—new "demi" strength permits dosage flexibility to meet each patient's specific needs. **PERCODAN-DEMI** provides the **PERCODAN** formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

**AVERAGE ADULT DOSE:** 1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

Each **PERCODAN-DEMI** Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

© 1974 Endo Labs



Amazing! The pain went away fast—in about 15 minutes. I slept like a baby. Finished my design for the new warehouse next day, and not a bit of trouble since!

## AND THE PAIN WENT AWAY FAST

**Endo<sup>®</sup>**

Literature? Write  
**ENDO LABORATORIES**  
Richmond Hill 18, New York

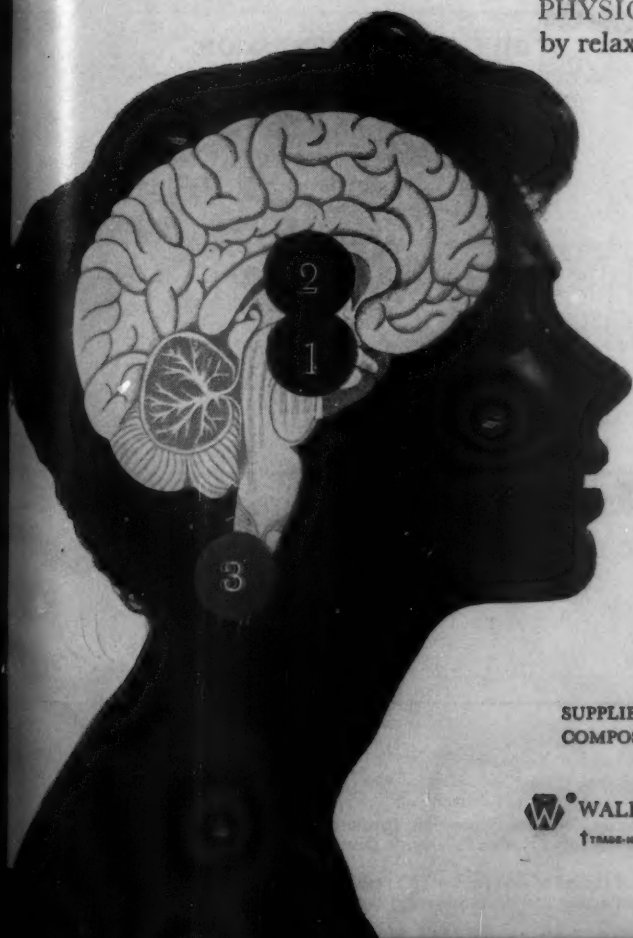
# COMPREHENSIVE, THREE-LEVEL TREATMENT OF DEPRESSION

AND ASSOCIATED ANXIETY  
AND PHYSICAL TENSION

RELIEVES DEPRESSION  
including symptoms such as crying,  
lethargy, loss of appetite, insomnia

RELIEVES ASSOCIATED ANXIETY  
with no risk of drug-induced depression

RELIEVES ASSOCIATED  
PHYSICAL TENSION  
by relaxing skeletal muscle



1  
hypothalamus

2  
thalamus and  
limbic system

3  
spinal cord

## Deprol<sup>†</sup>

benactyzine + meprobamate

- confirmed efficacy
- documented safety

SUPPLIED: Bottles of 50 light-pink, scored tablets

COMPOSITION: Each tablet contains 1 mg. benactyzine HCl  
and 400 mg. meprobamate



WALLACE LABORATORIES • New Brunswick, N. J.

<sup>†</sup> TRADE-MARK

CS-0300

# Tofrānil<sup>®</sup> a thymoleptic

brand of imipramine HCl

Specific in Depression

## does

Produce remission or improvement in  
70-85% of cases

Act effectively in all types of depression

Afford equally good results in severe  
as in mild cases

Achieve therapeutic benefit with minimal risk of  
serious side reaction

Indications for Tofrānil include:

Endogenous Depression, Reactive Depression, Involutional Melancholia, Senile Depression, Depression associated with other Psychiatric Disorders.

Availability: Tofrānil (brand of imipramine HCl) tablets of 25 mg. bottles of 100. Ampuls of 25 mg. (for intramuscular administration only) cartons of 10 and 50.

.....not a MAO inhibitor

does not

Inhibit monoamine oxidase either in brain or liver with its associated risks


Produce dangerous potentiation of other drugs such as barbiturates and alcohol

Act by producing undesirable central nervous stimulation leading to agitation and excitement

Cause disturbance of color vision

The efficacy of Tofranil is attested by more than 50 published reports and confirmed by clinical experience in more than 50,000 cases.

Detailed Literature Available on Request.

 Geigy, Ardsley, New York

**Geigy**

IN NAUSEA/VOMITING/VERTIGO



## SPECIFIC

and unnecessary  
to report diverse  
injection, alter-  
ing the economical  
and day usage

## UNCOMPLICATED

Has no known contraindications, free of hepatic, hypotensive, and hematologic hazards observed with phenothiazines

# BONINE\*

ANTHELMINTIC BONA-MINE

INDICATIONS

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

Roundworm, tapeworm, pinworm

PLEASE NOTE!

**BONINE\***  
(BON-EEN)

(FORMERLY CALLED

**BONAMINE)**

is the new name  
for the SAME  
superior product

Pfizer

LABORATORIES

**How many patients today  
complained about pain?**



non-narcotic—pain relief equivalent  
to that of codeine

well tolerated in both acute and  
prolonged use

wide range of indications—general  
practice and the specialties

analgesia plus anti-inflammatory  
action

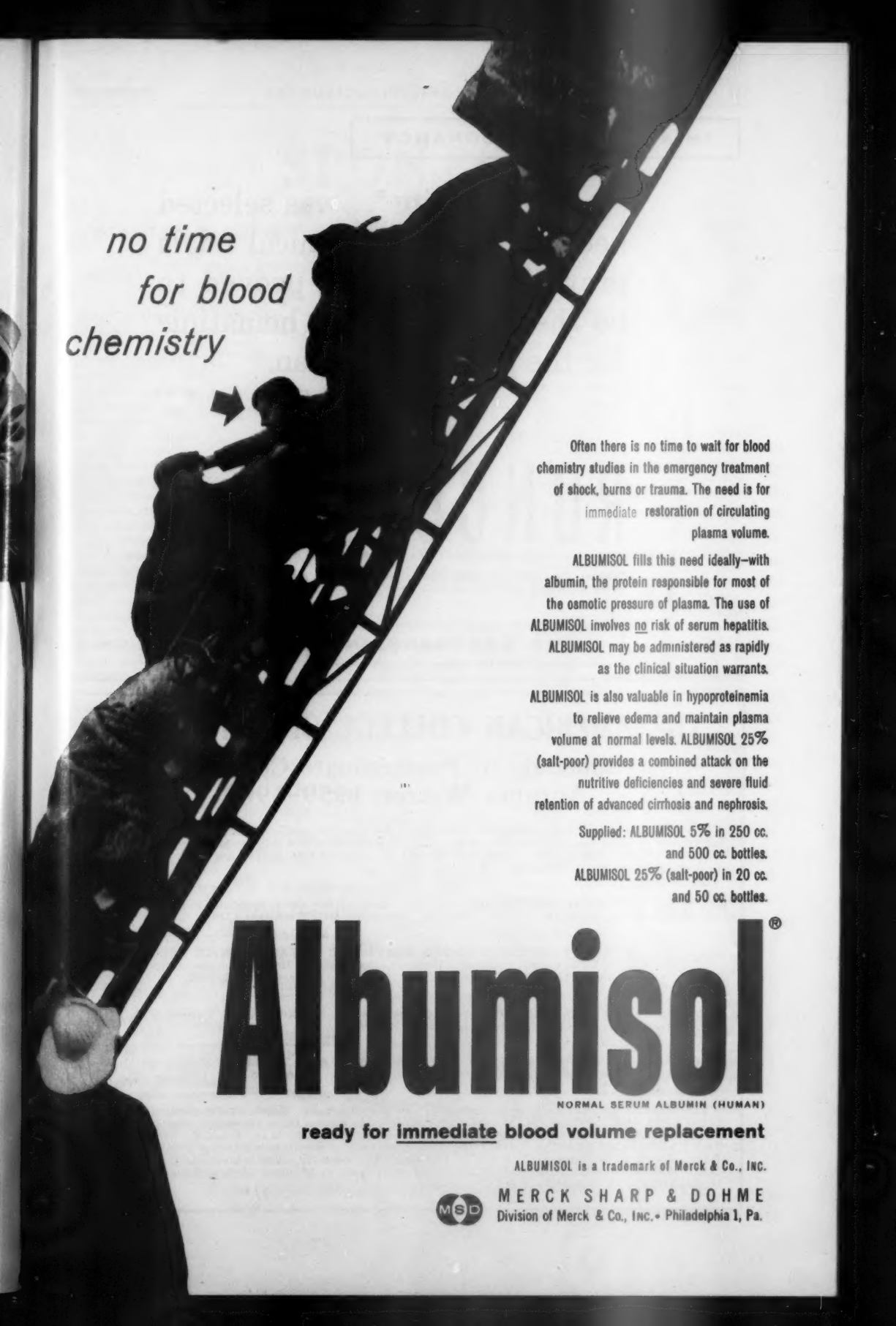
Supplied: Tablets, bottles of 48. Each tablet  
contains 75 mg. of ethoheptazine citrate and  
325 mg. (5 grains) of acetylsalicylic acid.

**remember**

**PAIN**  
**Zactirin**  
Ethoheptazine Citrate with Acetylsalicylic Acid, Wyeth



Philadelphia 1, Pa.



*no time  
for blood  
chemistry*

Often there is no time to wait for blood chemistry studies in the emergency treatment of shock, burns or trauma. The need is for immediate restoration of circulating plasma volume.

ALBUMISOL fills this need ideally—with albumin, the protein responsible for most of the osmotic pressure of plasma. The use of ALBUMISOL involves no risk of serum hepatitis.

ALBUMISOL may be administered as rapidly as the clinical situation warrants.

ALBUMISOL is also valuable in hypoproteinemia to relieve edema and maintain plasma volume at normal levels. ALBUMISOL 25% (salt-poor) provides a combined attack on the nutritive deficiencies and severe fluid retention of advanced cirrhosis and nephrosis.

Supplied: ALBUMISOL 5% in 250 cc.  
and 500 cc. bottles.

ALBUMISOL 25% (salt-poor) in 20 cc.  
and 50 cc. bottles.

# Albumisol<sup>®</sup>

NORMAL SERUM ALBUMIN (HUMAN)

**ready for immediate blood volume replacement**

ALBUMISOL is a trademark of Merck & Co., Inc.



**MERCK SHARP & DOHME**  
Division of Merck & Co., Inc. • Philadelphia 1, Pa.

**IN ANEMIA OF PREGNANCY**

Roncovite "...was selected because it has, in clinical trials previously reported, proved to be the most effective hematinic for the pregnant woman."

—Holly, R. G., and Grund, W. J.:  
*Am. J. Obstet. & Gynec.* 77:731 (April) 1959.

# RONCOVITE<sup>®</sup>-mf

Each tablet contains: Cobalt chloride (Cobalt as Co...3.7 mg.)...15 mg. Ferrous sulfate exsiccated...100 mg.

**Dosage:** The maximum adult dose of Roncovite-MF and Roncovite-OB is one tablet after each meal and at bedtime.

**LLOYD BROTHERS, INC.**

CINCINNATI 3, OHIO

## THE AMERICAN COLLEGE OF PHYSICIANS Schedule of Postgraduate Courses Autumn-Winter, 1959-1960

The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Customary tuition fees will be: Members, \$60.00; Non-members, \$80.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.

**Course No. 4, CLINICAL CARDIOLOGY:** Tulane University School of Medicine, New Orleans, La.; George E. Burch, Jr., M.D., F.A.C.P., Director. **November 30 to December 4, 1959.**

**Course No. 5, CURRENT CONCEPTS OF THE RHEUMATIC DISEASES—THEIR RECOGNITION AND MANAGEMENT:** Cornell University Medical College and The Hospital for Special Surgery, New York, N. Y.; Richard H. Freyberg, M.D., F.A.C.P., Director. **January 11 to 15, 1960.**

**Course No. 6, INTERNAL MEDICINE—Selected Subjects:** Henry Ford Hospital, Detroit, Mich.; John G. Mateer, M.D., F.A.C.P., Director. **January 25 to 29, 1960.**

**Course No. 7, RECENT ADVANCES IN METABOLIC DISEASES:** The Mount Sinai Hospital, New York, N. Y.; Alexander B. Gutman, M.D., F.A.C.P., Director. **February 8 to 12, 1960.**

The following courses are being organized to run simultaneously, March 21-25, 1960: **CURRENT CONCEPTS IN CLINICAL GASTROENTEROLOGY:** Louisiana State University and Tulane University Schools of Medicine, New Orleans, La.; G. Gordon McHardy, M.D., F.A.C.P., Director. **RECENT ADVANCES IN PHARMACOTHERAPY:** University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director. The following course is scheduled for April 25-29, 1960: **DERMATOLOGY FOR THE INTERNIST:** University of Michigan Medical School, Ann Arbor, Mich.; Arthur C. Curtis, M.D., F.A.C.P., Director.

# SPONTIN®

(Ristocetin, Abbott)

## A STATISTICAL REVIEW\* OF THREE HUNDRED THIRTY-THREE CASES

\*Records of Medical Department, Abbott Laboratories, North Chicago, Illinois

**S**PONTIN (Ristocetin, Abbott) is a new antibiotic discovered and developed at Abbott Laboratories.

Its two components, A and B, have been isolated in a pure state from the fermentation of a new species of *Nocardia lurida*. Both are active against gram-positive bacteria and mycobacteria. A mycete was isolated from a sample collected from the lungs of a patient from the Goddard, Colorado Sanatorium. No other culture which has the same antibiotic has been reported.

The chemical characteristics of ristocetins are not completely known, although they are known to be heterocyclic substances containing phenolic groups. Ristocetin A and B are molecules with molecular weights in the vicinity of 4000. They have good stability in solution over a pH range of blood. SPONTIN is a lyophilized preparation, derived from the same material, representing ristocetins A and B.

Antimicrobial activity against gram-positive organisms, SPONTIN is more effective than most available antibiotics.

Against pneumococci (except *S. pneumoniae*) the antibiotic is bactericidal at the concentration which inhibits the growth of the organism. It also kills the organism in the blood.

This observation is of importance for the major staphylococcal infections. However, staphylococci have been tested at a concentration of minimum 1:1000 and produce a bacteriostatic effect at this reason.

SPONTIN is used for the treatment of staphylococcal and enterococcal infections.

Cultures of staphylococcus aureus, which are resistant to other anti-

otics have been shown to be sensitive to SPONTIN. There has been no case reported in which a staphylococcal or enterococcal strain has exhibited a

SPONTIN

tion, derived from pure crystalline material, representing a mixture of ristocetins A and B.

Antimicrobial Properties. In its action against gram-positive cocci or bacilli, SPONTIN is notably more effective than most currently avail-

### Summary and Conclusions

Major use has been treating staphylococcal infections. Of the total 333 cases, approximately one-third was treated for pneumonia; of these over 80% were either cured or improved. About 70% of these pneumonias were caused by staphylococci.

The next largest group included 46 patients with subacute bacterial endocarditis. About 50% of these infections were identified as staphylococcal and a further 15% as enterococcal. Other infections included 38 cases of septicemia, 32 abscesses and 24 patients with osteomyelitis.

The administration of SPONTIN brought about a cure in 60% of all the cases reviewed and improvement in a further 17%.

Side-effects were seldom troublesome when a daily dose of 2 Gm. was not exceeded. The incidence rose as the dosage was increased. The most disturbing side-effect after administration of SPONTIN has been neutropenia. However, in all instances this has responded to either discontinuance of medication or reduction in dose.

and streptococci of enterococcal origin. The concentration of which in organisms

holds true of staphylococcal strains of cocci which required a concentration higher than the recommended concentration to effect. It is for this reason that the dosage of recommended staphylococcal infections.

*S. aureus*, to other antibiotics to be sensitive has been no case of staphylococcal or enterococcal has exhibited a SPONTIN.

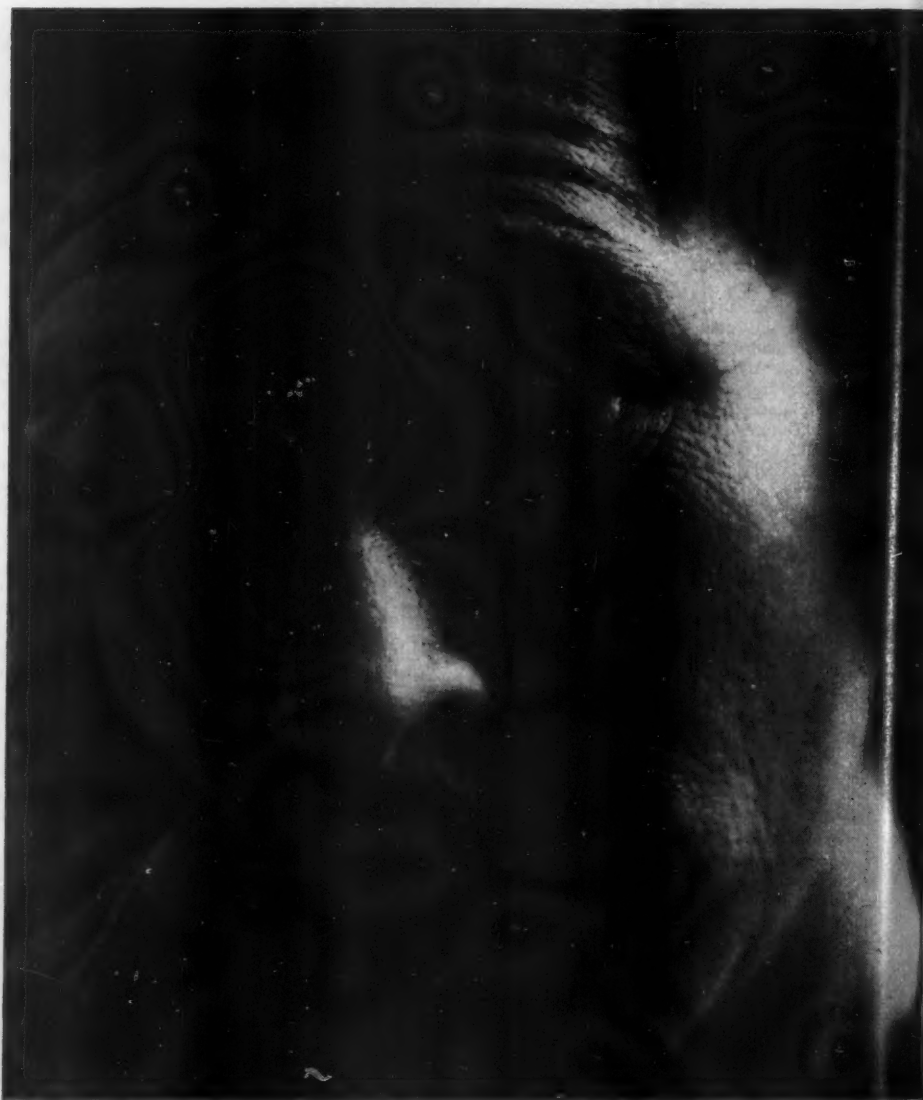
that the antibiotic is enhanced by gamma globulin. This is supported by the *in vivo* activity of SPONTIN which is greater than that from the *in vitro*

investigators\* have reported a good response following administration of SPONTIN. Studies have shown a bacteriostatic effect on the part of the organism. Satisfactory results may be expected in cases requiring up to 25 Gm. of SPONTIN for inhibition. The following table shows the sensitivities of different strains of the major pathogenic

V000004

# FOR ANXIETY

—particularly when  
expressed as apathy, listlessness and emotional fatigue



## TYPICAL PRESENTING SYMPTOMS

loss of normal drive  
inability to concentrate  
or work effectively  
indecisiveness  
irritability  
crying spells

insomnia  
anorexia  
vague fears  
undue preoccupation  
with somatic complaints  
wide swings of mood

generalized discomfort  
headaches  
dizziness  
palpitations  
hyperventilation  
epigastric distress

# NEW

## 1 mg. STELAZINE\* TABLETS

brand of trifluoperazine

'Stelazine' is unique because it not only relieves agitation and tension, but also relieves apathy, listlessness and emotional fatigue resulting from anxiety states.

Other noteworthy characteristics of 'Stelazine', brought out in clinical studies in over 12,000 patients, are:

- \* effectiveness where other agents fail
- \* notable lack of troublesome side effects
- \* fast therapeutic response with very low doses
- \* convenient b.i.d. administration

"THE INDIFFERENCE WHICH OCCURS COMMONLY WITH OTHER TRANQUILIZERS WAS ABSENT."<sup>1</sup>

This observation about 'Stelazine' points to what may be one of the most important and distinguishing characteristics of the drug—that is, 'Stelazine', while relieving emotional distress, does not "tranquilize" your patients out of normal activity or normal aims.

AVAILABLE for use in everyday practice—1 mg. tablets, in bottles of 50 and 500. Literature available on request. Smith Kline & French Laboratories, Philadelphia.

REFERENCES: 1. Gearren, J.B.: *Dis. Nerv. System* 20:66 (Feb.) 1959. 2. Margolis, E.J.; Pauley, W.G.; Cauffman, W.J., and Gregg, P.C.: Scientific Exhibit at the 12th Clinical Meeting of the American Medical Association, Minneapolis, Minn., Dec. 2-5, 1958. 3. Phillips, F.J., and Shoemaker, D.M.: *ibid.* 4. Ayd, F.J., Jr.: *Clin. Med.* 6:387 (Mar.) 1959.

SMITH  
KLINE &  
FRENCH

\*Trademark

leaders in psychopharmaceutical research

## INDEX TO ADVERTISERS NOVEMBER, 1959

Abbott Laboratories .....	Insert facing 32, 48, 79, 88, 100-101, 173
Air Mass, Inc. ....	112
American Cancer Society .....	4
A. C. P. Gifts .....	104
A. C. P. Postgraduate Courses .....	172
A. C. P. Sessions .....	6
Ames Company, Inc. ....	158-159
A. I. M. Subscriptions .....	156
A. I. M. Wanted Back Issues .....	4, 160
Armour Pharmaceutical Products, Inc. ....	82
Astra Pharmaceutical Products, Inc. ....	137
Ayerst Laboratories .....	41, 76-77
Borchardt Company .....	44
Burdick Corporation .....	60
Burton, Parsons & Company .....	94
Cambridge Instrument Company, Inc. ....	153
Carnation Milk Company .....	116
Ciba Pharmaceutical Products, Inc. ....	2-9, 57, 100-100, 142
Davies Rose & Company, Limited .....	128
Dome Chemical Company .....	40
Eaton Laboratories .....	47, 49, 90, 134-135
Endo Laboratories .....	50-51, 164
E. Fougere and Company .....	133, 161
Geigy Chemical Corporation .....	24, 53, 64, 106, 106-107
General Electric Company .....	102
Harvard University Press .....	6
Paul B. Hoeber, Inc. ....	5
Hyland Laboratories .....	43
Irwin Neisler & Company .....	124
Knoll Pharmaceutical Company .....	65
Lakeside Laboratories, Inc. ....	42, 141
LaMotte Chemical Products Company .....	44
Lea & Febiger .....	4
Lederle Laboratories, Div. American Cyanamid Co. ....	16-17, 105, 162-163
Thos. Leeming & Company .....	2, 157
Ell Lilly & Company .....	Third Cover
Lloyd Brothers, Inc. ....	70, 123, 172
Macmillan Company, The .....	1
Mallinckrodt Chemical Works .....	121
McNeill Laboratories, Inc. ....	14, 139
Mead Johnson & Company .....	10, 22-23, 52
Merck Sharp & Dohme .....	26-27, 84-85, 98, 117, 120, 154-155, 171
Wm. S. Merrill Company, The .....	72
National Tuberculosis Association .....	42
Organon, Inc. ....	22-29
Pfizer Laboratories, Div. Chas. Pfizer Co. Inc. ....	Insert facing 80, 20, 113, 168-169
Pharmacia Laboratories, Inc. ....	115
Pitman-Moore Company .....	38, 129
Michael Reese Hospital .....	6
Riker Laboratories .....	Second Cover, 178
A. H. Robins Company .....	36, 87
Roche Laboratories, Div. Hoffmann LaRoche, Inc. ....	15, 30, 110-111, 143
J. B. Roerig & Company .....	39, 62-63, 130-131
Wm. H. Rorer, Inc. ....	78
Sanborn Company .....	74
Sandoz Pharmaceuticals .....	122-123
W. B. Saunders Company .....	3
Schering Corporation .....	42, 61, 71, 81, 95, 119, 141
G. D. Searle & Co. ....	97
Smith, Kline & French Laboratories .....	73, 126-127, 174-175
E. R. Squibb & Sons, Div. Olin Mathieson Chemical Corp. ....	11, 25, 66, 86, 91, 107, 120
R. J. Strassenburgh Co. ....	144-145, 146
Training School, The .....	44
Travenol Laboratories, Inc., Div. Baxter Laboratories, Inc. ....	99
Upjohn Company, The .....	37, 136
U. S. Vitamin Corporation .....	Insert facing 64
Wallace Laboratories .....	18, 21, 34-35, 82, 89, 125, 132, 141, 150, 165
Wampole Laboratories .....	38
Warner-Chilcott Laboratories .....	7, 45, 54-55, 75, 92, 140, 147, 149, 151
Warren-Teed Products, Inc. ....	31
William A. Webster Company .....	100
White Laboratories .....	Insert facing 106, 67, 68-69
Winthrop Laboratories, Inc. ....	56, 83, 103
Woodward Medical Personnel Bureau .....	160
Wyeth Laboratories .....	12-13, 19, 46, 56-59, 80, 93, 114, 118, 138, 152, 170, 177
Wynn Pharmacal Corporation .....	148

Please Mention this Journal when writing to Advertisers

In your everyday practice, PROZINE helps control moderate to severe emotional disturbance manifested by apprehension and agitation or associated:

- nausea and vomiting
- insomnia
- depression (with anxiety)
- premenstrual tension
- alcoholism
- menopausal symptoms

PROZINE acts upon both the thalamic and hypothalamic areas of the brain; controls anxiety and tension as well as psychomotor agitation.

*Controls psychomotor agitation, anxiety and tension*



# PROZINE\*

meprobamate and promazine hydrochloride, Wyeth

SPECIFIC CONTROL THROUGH DUAL ACTION



\*Trademark

Philadelphia 1, Pa.

Please Mention this Journal when writing to Advertisers

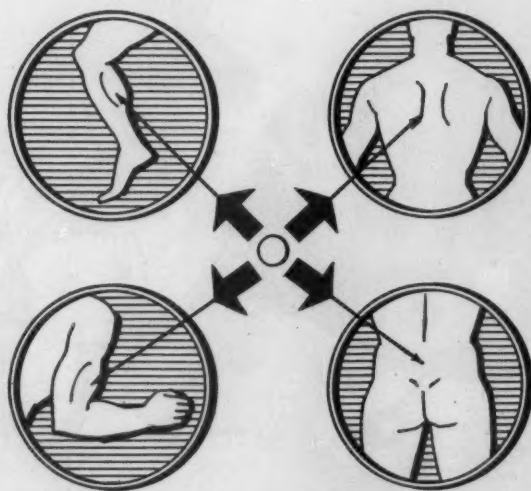
## *In Skeletal Muscle Spasm*

# Norflex<sup>TM</sup>

orphenadrine citrate

*acts quickly to restore mobility and  
afford relief of associated pain*

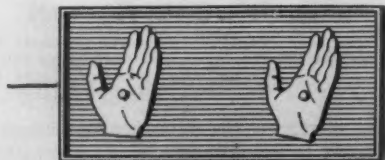
*Spasmolytic action  
is prompt, and only the  
muscle in spasm is re-  
laxed...the patient is  
spared impairment of  
general muscle tonus.*



Patients can cooperate readily...the dosage is easily remembered: just one tablet b.i.d.

Compare this with other spasmolytics requiring from 4 to 30 tablets per day.

The action of Norflex is rapid and the effect is prolonged. SUPPLY: White unscored 100 mg. tablets in bottles of 50.



Only one tablet b.i.d. for all adults, regardless of age, weight, sex, or spasm severity.

**Riker** Northridge, California

\*Trademark U. S. Patent No. 2,997,961  
Other Patents Pending



relief from  
all sorts of  
influenza

## **DARVON® COMPOUND** potent • safe • well tolerated

Combines, in a single Pulvule®, the analgesic action of Darvon® (dextro propoxyphene hydrochloride, Lilly) with the antipyretic and anti-inflammatory benefits of A.S.A.\* Compound (acetylsalicylic acid and acetophenetidin compound, Lilly).

Darvon Compound obviates the need for a narcotic prescription.

Usual dosage for Darvon Compound is 1 or 2 Pulvules three or four times daily.

Also available: Darvon, in 32 and 65-mg. Pulvules. Usual dosage is 32 mg. every four hours or 65 mg. every six hours.

Darvon® Compound (dextro propoxyphene and acetylsalicylic acid compound, Lilly)

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

# ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

## EDITOR

MAURICE C. PINCOFFS, M.D., Baltimore

## ASSOCIATE EDITOR

PAUL W. CLOUGH, M.D., Baltimore

## ASSISTANT EDITOR

FRED R. MCCRUMB, M.D., Baltimore

## COMMITTEE ON PUBLICATIONS

CHESTER M. JONES, M.D., Boston, Chairman

WRIGHT ADAMS, M.D., Chicago; ALEX. M. BURGESS, SR., M.D., Providence;

A. CARLTON ERNSTENE, M.D., Cleveland; THOMAS FINDLEY, M.D., Augusta;

RICHARD A. KERN, M.D., Philadelphia; DWIGHT L. WILBUR, M.D., San Francisco

## EXECUTIVE SECRETARY

EDWARD R. LOVELAND, Philadelphia

Editorial Office—University Hospital, Baltimore 1, Maryland

Executive Office—4200 Pine Street, Philadelphia 4, Pa.

Place of Publication—Prince & Lemon Sts., Lancaster, Pa.

**MANUSCRIPTS.** All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. Bibliographic references are to conform to the following style:

4. Doe, J. T.: What I know about it. J. A. M. A. 96: 2006, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

**REPRINTS.** For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

**REVIEWS.** Selected monographs and books in the field of internal medicine will be reviewed monthly in the ANNALS. Authors and publishers wishing to submit such material should send it to the Editor. Since it is not possible to review all books submitted, a monthly list of all those received will be published in the review section.

**SUBSCRIPTION.** This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscription price per annum, net postpaid: \$10.00, United States, Canada, Hawaii, and Puerto Rico; \$7.00, in the above countries, to bona fide medical students, interns and residents; \$12.00, other countries. Prices for back numbers furnished upon application. Single numbers, current volume, when available, \$1.25. Checks should be drawn to the order of THOMAS M. DURANT, M.D., Treasurer, and remitted through the Executive Secretary's Office.

**BUSINESS CORRESPONDENCE.** All correspondence relating to business matters, advertising, subscriptions to the ANNALS, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

